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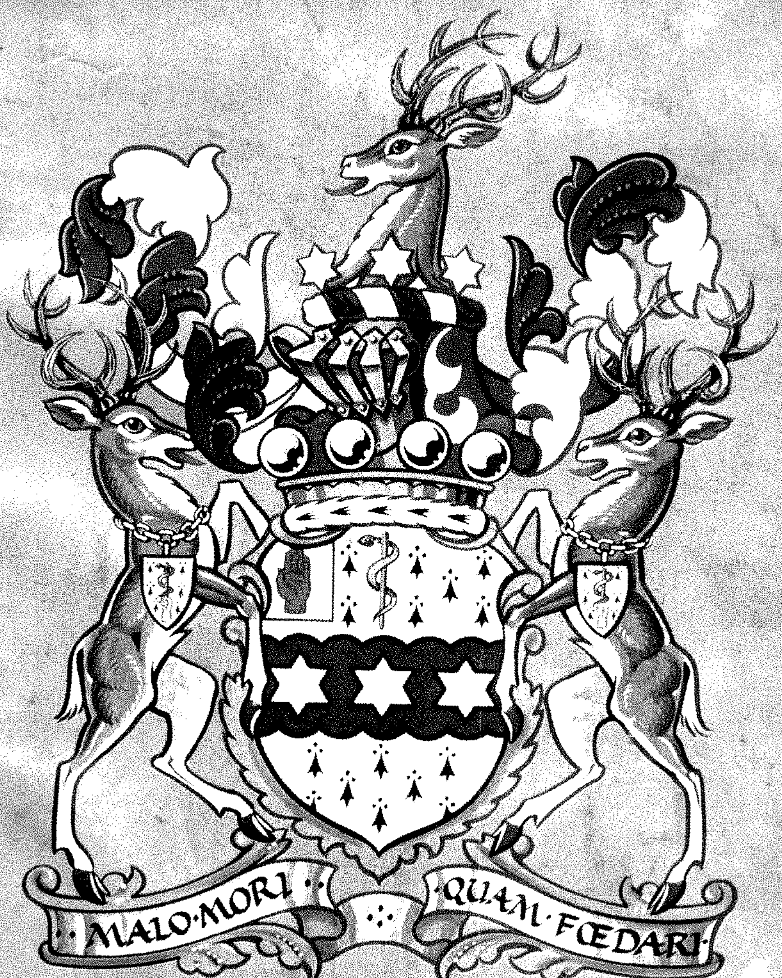

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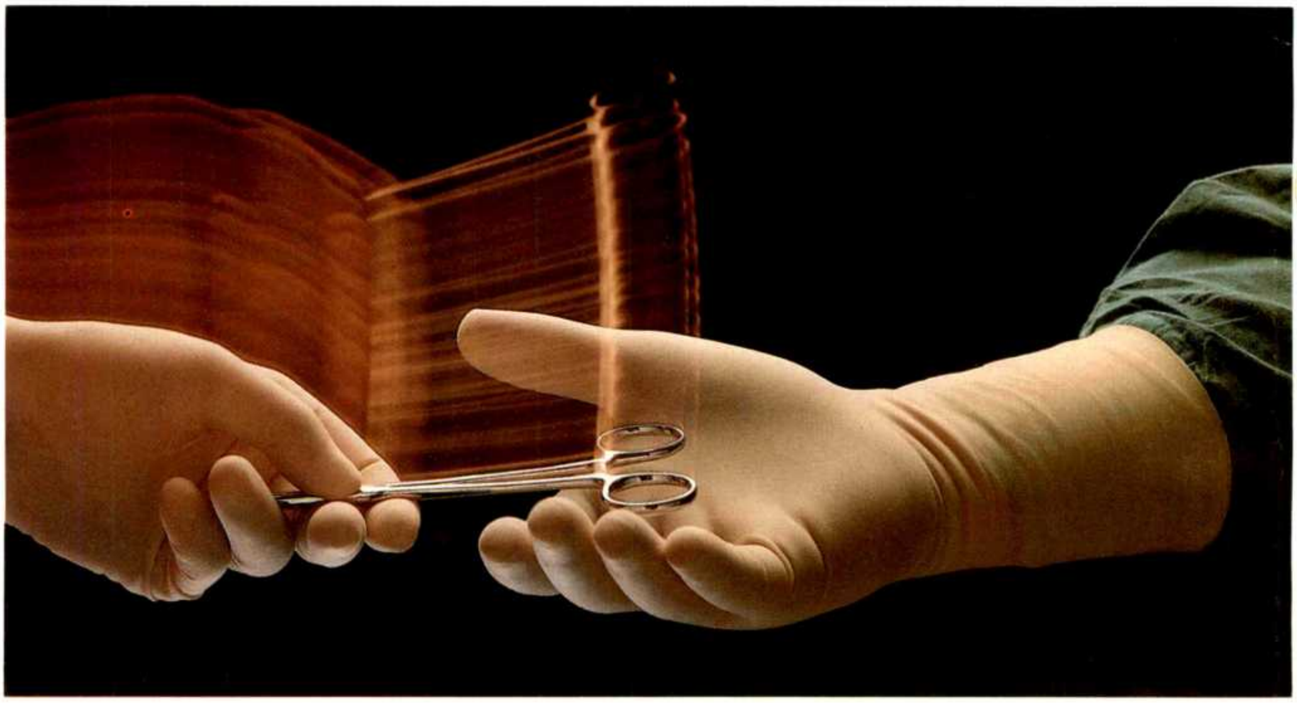

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Volume 78 Number 2 February 1991

LEADING ARTICLES

Mucosectomy in restorative proctocolectomy **129**
P. R. O'Connell and N. S. Williams

Laparoscopic cholecystectomy **131**
S. Paterson-Brown, O. J. Garden and D. C. Carter

REVIEWS

Surgical strategies in the treatment of pancreatic necrosis and infection **133**
A. D'Egidio and M. Schein

Merkel cell tumour: clinical behaviour and treatment **138**
J. H. F. Shaw and E. Rumball

New trends in gallstone management **143**
S. Cheslyn-Curtis and R. C. G. Russell

Conventional *versus* laparoscopic cholecystectomy and the randomized controlled trial **150**
E. Neugebauer, H. Troidl, W. Spangenberger, A. Dietrich, R. Lefering and The Cholecystectomy Study Group

Laparoscopic cholecystectomy: the Dundee technique **155**
L. K. Nathanson, S. Shimi and A. Cuschieri

Reduced postoperative hospitalization after laparoscopic cholecystectomy **160**
P. A. Grace, A. Quereshi, J. Coleman, R. Keane, G. McEntee, P. Broe, H. Osborne and D. Bouchier-Hayes

Piezoelectric lithotripsy for gallstones: analysis of results in patients with extended selection **163**
A. Darzi, E. El-Sayed, C. O'Morain, W. A. Tanner and F. B. V. Keane

Role of fine catheter peritoneal cytology and laparoscopy in the management of acute abdominal pain **167**
R. J. Baigrie, Z. Saidan, D. Scott-Coombes, J. B. Hamilton, M. Katesmark, M. N. Vipond, S. Paterson-Brown and J. N. Thompson

Population-based study of surgery in juvenile onset Crohn's disease **171**
D. M. Sedgwick, J. R. Barton, D. W. Hamer-Hodges, S. J. Nixon and A. Ferguson

Population-based study of surgery in juvenile onset ulcerative colitis **176**
D. M. Sedgwick, J. R. Barton, D. W. Hamer-Hodges, S. J. Nixon and A. Ferguson

Natural history of indeterminate colitis **179**
A. D. Wells, I. McMillan, A. B. Price, J. K. Ritchie and R. J. Nicholls

Changing pattern of intestinal obstruction in Malaysia: a review of 100 consecutive cases (short note) **181**
S. H. Lee and E. T. L. Ong

Outcome after emergency surgery for cancer of the large intestine **183**
N. S. Runkel, P. Schlag, V. Schwarz and C. Herfarth

Hirschsprung's disease presenting as neonatal gastrointestinal perforation (case report) **188**
M. D. Stringer and D. P. Drake

Non-steroidal anti-inflammatory drugs and complicated diverticular disease: a case–control study **190**
K. Campbell and R. J. C. Steele

Role of intraoperative enteroscopy in obscure gastrointestinal bleeding of small bowel origin **192**
L. A. Desa, S. K. Ohri, K. A. R. Hutton, H. Lee and J. Spencer

Risk of peritonitis and fatal septicaemia and the need to defunction the low anastomosis **196**
N. D. Karanjia, A. P. Corder, P. J. Holdsworth and R. J. Heald

Comparison of restorative proctocolectomy with and without covering ileostomy in ulcerative colitis **199**
H. J. Järvinen and P. Luukkonen

Principal causes of mechanical bowel obstruction in surgically treated adults in Western Turkey 202
M. Füzün, E. Kaymak, Ö. Harmancioğlu and K. Astarcioğlu

Reoperations for late complications following abdominal aortic operation 204
D. C. Haiart, M. J. Callam, J. A. Murie, C. V. Ruckley and A. McL. Jenkins

Light reflection rheography: an effective non-invasive technique for screening patients with suspected deep venous thrombosis 207
P. R. S. Thomas, C. M. Butler, J. Bowman, N. W. T. Grieve, C. E. Bennett, R. S. Taylor and M. H. Thomas

Histological study of white blood cells and their association with lipodermatosclerosis and venous ulceration 210
H. J. Scott, P. D. Coleridge Smith and J. H. Scurr

Oesophageal transection and oesophagogastric devascularization in patients with thrombophilia and oesophageal varices (case report) 212
B. E. Kelly, I. Watt and J. R. Anderson

Long-term follow-up of elderly patients with locoregional breast cancer treated with tamoxifen only 213
J. M. Horobin, P. E. Preece, J. A. Dewar, R. A. B. Wood and A. Cuschieri

Mammography in the management of patients with small breast cancers 218
J. M. Dixon and U. Chetty

Gunshot wound of the abdomen: role of selective conservative management 220
D. Demetriades, D. Charalambides, M. Lakhoo and D. Pantanowitz

Abdominal wall tenderness: a useful sign in chronic abdominal pain 223
W. H. F. Thomson, R. F. H. Dawes and S. St. C. Carter

Horizontal testis with a varicocele: a new physical sign (short note) 225
R. A. Wheeler and J. D. Atwell

Cytoreductive surgery in disseminated non-seminomatous germ cell tumours of testis 226
R. P. Kulkarni, K. W. Reynolds, E. S. Newlands, P. M. Dawson, A. R. Makey, N. A. Theodorou, J. Bradley, R. H. J. Begent, G. J. S. Rustin and K. D. Bagshawe

Major trauma: a district general hospital experience 230
C. L. Ingham Clark and M. Tabone-Vassallo

Long-term survival in patients operated on for benign peptic ulcer disease 234
G. Lundegårdh, L. Holmberg and U. B. Krusemo

Effects of cardiac surgery and intraoperative hypothermia on energy expenditure as measured by doubly labelled water 237
D. P. Taggart, D. C. McMillan, T. Preston, R. Richardson, H. J. G. Burns and D. J. Wheatley

Massive incisional hernia: abdominal wall replacement with Marlex® mesh 242
R. G. Molloy, K. T. Moran, R. P. Waldron, M. P. Brady and W. O. Kirwan

Where there is no anaesthetist... 245
A. K. Leppäniemi

Management of disc battery ingestion in children (case report) 247
N. El-Barghouty

CORRESPONDENCE 248

BOOK REVIEWS 253

NOTICES AND ANNOUNCEMENTS 254

SURGERY AND THE AMERICAN JOURNAL OF SURGERY CONTENTS 255

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The British Journal of Surgery

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Volume 78 Number 6 June 1991

LEADING ARTICLES

Angioplasty for mild intermittent claudication 643
M. R. Whyman, C. V. Ruckley and F. G. R. Fowkes

Invasive breast cancer – where now? 646
A. P. M. Forrest and H. J. Stewart

REVIEWS

Influence of local recurrence on survival: a controversy reviewed from the perspective of soft tissue sarcoma 648
L. C. Barr, A. T. Stotter and R. P. A'Hern

Pathophysiology of ischaemia reperfusion injury: central role of the neutrophil 651
C. R. B. Welbourn, G. Goldman, I. S. Paterson, C. R. Valeri, D. Shepro and H. B. Hechtman

Endothelial cell seeding 656
D. A. Mosquera and M Goldman

Results of the Duhamel operation in the treatment of idiopathic megarectum and megacolon 661
G. Stabile, M. A. Kamm, P. R. Hawley and J. E. Lennard-Jones

Intraoperative localization of colorectal cancers using radiolabelled monoclonal antibodies 664
B. R. Davidson, W. A. Waddington, M. D. Short and P. B. Boulos

Suture technique affects perianastomotic colonic crypt cell production and tumour formation 671
A. F. O'Donnell, P. R. O'Connell, D. Royston, D. H. Johnston, R. Barnard and D. Bouchier-Hayes

Clinical presentation of dracontiasis (short note) 674
S. E. E. Efem

Pyoderma gangrenosum in inflammatory bowel disease 676
M. D. Levitt, J. K. Ritchie, J. E. Lennard-Jones and R. K. S. Phillips

Strategy for management of distal ileal Crohn's disease 679
H. A. Andrews, M. R. B. Keighley, J. Alexander-Williams and R. N. Allan

Encysted pneumatocele: a complication of diverticular disease (case report) 683
A. J. Ritchie, J. G. Carson and W. G. Humphreys

Devine exclusion for unresectable carcinoma of the stomach 684
S. P. Y. Kwok, S. C. S. Chung, S. M. Griffin and A. K. C. Li

Optimum duration of surgical scrub-time (short note) 685
M. O'Shaughnessy, V. P. O'Malley, G. Corbett and H. F. Given

Perineal excision of the rectum for prolapse in the elderly 687
I. G. Finlay and M. Aitchison

Anismus in patients with normal and slow transit constipation 690
R. Miller, G. S. Duthie, D. C. C. Bartolo, A. M. Roe, J Locke-Edmunds and N. J. McC. Mortensen

Relationship between outlet obstruction constipation and obstructed urinary flow 693
A. MacDonald, M. Shearer, P. J. Paterson and I. G. Finlay

Evaluation of diagnostic peritoneal lavage in suspected penetrating abdominal stab wounds using a dipstick technique 696
D. J. J. Muckart and M. A McDonald

Early abdominal complications following heart and heart–lung transplantation 699
C. J. E. Watson, N. V. Jamieson, P. S. Johnston, T. Wreghitt, S. Large, J. Wallwork and T. A. H. English

Suture length to wound length ratio and the integrity of midline and lateral paramedian incisions 705
S. W. H. Kendall, T. G. Brennan and P. J. Guillou

Synthesis of collagen types I and III in reincised wounds in humans 708
K. Haukipuro

Autologous transfusion: an alternative to transfusion with banked blood during surgery for cancer 713
G. V. Miller, C. W. Ramsden and J. N. Primrose

Severe late postsplenectomy infection 716
G. L. Cullingford, D. N. Watkins, A. D. J. Watts and D. F. Mallon

Paget's disease of the nipple 722
A. R. Dixon, M. H. Galea, I. O. Ellis, C. W. Elston and R. W. Blamey

Deep vein thrombosis: effect of graduated compression stockings on distension of the deep veins of the calf 724
P. D. Coleridge Smith, J. H. Hasty and J. H. Scurr

Combined portal vein and liver resection for carcinoma of the biliary tract 727
Y. Nimura, N. Hayakawa, J. Kamiya, S. Maeda, S. Kondo, A. Yasui and S. Shionoya

Intra-arterial streptokinase infusion in acute lower limb ischaemia 732
D. J. A. Scott, M. G. Wyatt, Y. G. Wilson, P. Murphy, R. N. Baird and M. Horrocks

Consequences of radial and ulnar artery ligation following trauma (short note) 735
M. O'Shaughnessy, D. S. O'Riordain, J. McCann, T. P. O'Connor and K. C. Condon

Angiographic embolization of intrahepatic arterioportal fistula (case report) 736
J. M. Romeo, N. Herrera and L. Perez Picouto

SURGICAL RESEARCH SOCIETY ABSTRACTS A738

CORRESPONDENCE 760

BOOK REVIEWS 764

NOTICES AND ANNOUNCEMENTS 765

SURGERY AND THE AMERICAN JOURNAL OF SURGERY CONTENTS 766

The British
Journal of Surgery

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Volume 78 Number 7 July 1991

LEADING ARTICLE

Intra-arterial chemotherapy for breast cancer **769**
R. Sainsbury

REVIEWS

Improving survival in gastric cancer: review of operative mortality in English language publications from 1970 **771**
I. M. C. Macintyre and J. C. Akoh

Statistical aspects of research methodology **777**
G. D. Murray

Statistical guidelines for *The British Journal of Surgery* **782**
G. D. Murray

Accuracy of endosonography in the staging of rectal cancer treated by radiotherapy **785**
B. Napolean, B. Pujol, F. Berger, P. J. Valette, J. P. Gerard and J. C. Souquet

Comparison of morbidity and function after colectomy with ileorectal anastomosis or restorative proctocolectomy for familial adenomatous polyposis **789**
M. V. Madden, K. F. Neale, R. J. Nicholls, J. C. Landgrebe, P. D. Chapman, H. J. R. Bussey and J. P. S. Thomson

Use of the ultrathin choledochoscope in cholecystectomy **793**
P. S. Rooney, D. C. Wherry, D. L. Morris and J. Doran

Rebound tenderness test **795**
M. I. Liddington and W. H. F. Thomson

One hundred patients with hepatic metastases from colorectal cancer treated by resection: analysis of prognostic determinants **797**
R. Doci, L. Gennari, P. Bignami, F. Montalto, A. Morabito and F. Bozzetti

Controlled hepatic bipartition for transplantation in children (case report) **802**
D. Houssin, C. Couinaud, O. Boillot, J. Laurent, N. Habib, M. Matmar, C. Vigouroux, D. Devictor and Y. Chapuis

Surgical anatomy of donor extended right trisegmentectomy before orthotopic liver transplantation in children **805**
K. C. Tan, G. P. Malcolm, A. S. Reece and R. Y. Calne

Extracorporeal shock wave treatment of common bile duct stones: experience with two different lithotriptors at a single institution **809**
R. den Toom, H. G. T. Nijs, M. van Blankenstein, J. S. Lamèris, F. H. Schroder and O. T. Terpstra

Successful reuse of a liver graft (case report) **813**
E. G. Moreno, G. I. García, I. González-Pinto, S. R. Gómez and S. C. Loinaz

Results of surgery for duodenal ulcer: assessment by patients **815**
P. D. Stanton and J. R. Anderson

Problems in the definition and treatment of early gastric cancer **818**
K. Inoue, T. Tobe, N. Kan, Y. Nio, M. Sakai, E. Takeuchi and T. Sugiyama

Surgical treatment of carcinoma of the gastric stump **822**
M. Sasako, K. Maruyama, T. Kinoshita and K. Okabayashi

Lymph node counts in the upper abdomen: anatomical baasis for lymphadenectomy in gastric cancer **825**
P. K. Wagner, A. Ramaswamy, J. Rüschoff, P. Schmitz-Moormann and M. Rothmund

Clinical significance of the large adrenal mass 828
F. A. Khafagi, M. D. Gross, B. Shapiro, G. M. Glazer, I. Francis and N. W. Thompson

Success and failure with neonatal tracheo-oesophageal anomalies 834
D. W. Goh and R. J. Brereton

Necrotizing fasciitis 838
S. K. Asfar, A. Baraka, T. Juma, A. Ma'Rafie, T. Aladeen and H. Al Sayer

Effect of fibrin glues on the mechanical properties of healing wounds 841
D. J. Byrne, J. Hardy, R. A. B. Wood, R. McIntosh and A. Cuschieri

Node negative breast cancer: the prognostic value of DNA ploidy for long-term survival 844
J. Yuan, C. Hennessy, I. P. Corbett, R. Dykin, A. L. Givan, B. K. Shenton, J. A. Henry, C. Wright and T. W. J. Lennard

Autopsy-verified pulmonary embolism in a surgical department: analysis of the period from 1951 to 1988 849
B. Lindblad, A. Eriksson and D. Bergqvist

Fibrinolytic activity of the arms and legs of patients with lower limb venous disease 853
H. Gajraj and N. L. Browse

Time trends in incidence rates of acute, non-traumatic extremity ischaemia: a population-based study during a 19-year period 857
C. Ljungman, H.-O. Adami, D. Bergqvist, A. Berglund and I. Persson

Realistic expectations for the patient with intermittent claudication 861
D. S. O'Riordain and J. A. O'Donnell

Epidemiology of chronic venous ulcers 864
S. R. Baker, M. C. Stacey, A. G. Jopp-McKay, S. E. Hoskin and P. J. Thompson

Influence of phlebographic abnormalities on the natural history of venous ulceration 868
M. C. Stacey, K. G. Burnand, M. Lea Thomas and M. Pattison

Early computed colour echo Doppler imaging following renal transplantation 872
M. R. Rajaseker, J. P. A. Lodge, H. C. Irving and G. R. Giles

Preoperative clinical evaluation as a predictor of cardiac complications after infrarenal aortic reconstruction 875
L. Chadwick and R. B. Galland

Effects of two methods of endothelial cell seeding on cell retention during blood flow 878
J. S. Budd, K. E. Allen and P. R. F. Bell

Streptococcus bovis septicaemia associated with uncomplicated colonic carcinoma (short note) 883
A. J. McMahon, C. D. Auld, B. A. S. Dale, A. D. F. Walls and J. C. StC. McCormick

Major limb amputation in northern Nigeria (short note) 885
C. Holcombe and S. Hassan

Isolated testicular pain: an unrecognized symptom of the leaking aortic aneurysm (case report) 886
S. J. Cawthorn, A. E. B. Giddings, R. S. Taylor and M. H. Thomas

Torsion of the spleen managed by splenopexy 887
B. J. Jones, M. Daly and P. V. Delaney

ERRATUM 888

CORRESPONDENCE 889

BOOK REVIEWS 892

NOTICES AND ANNOUNCEMENTS 895

AMERICAN JOURNAL OF SURGERY CONTENTS 896

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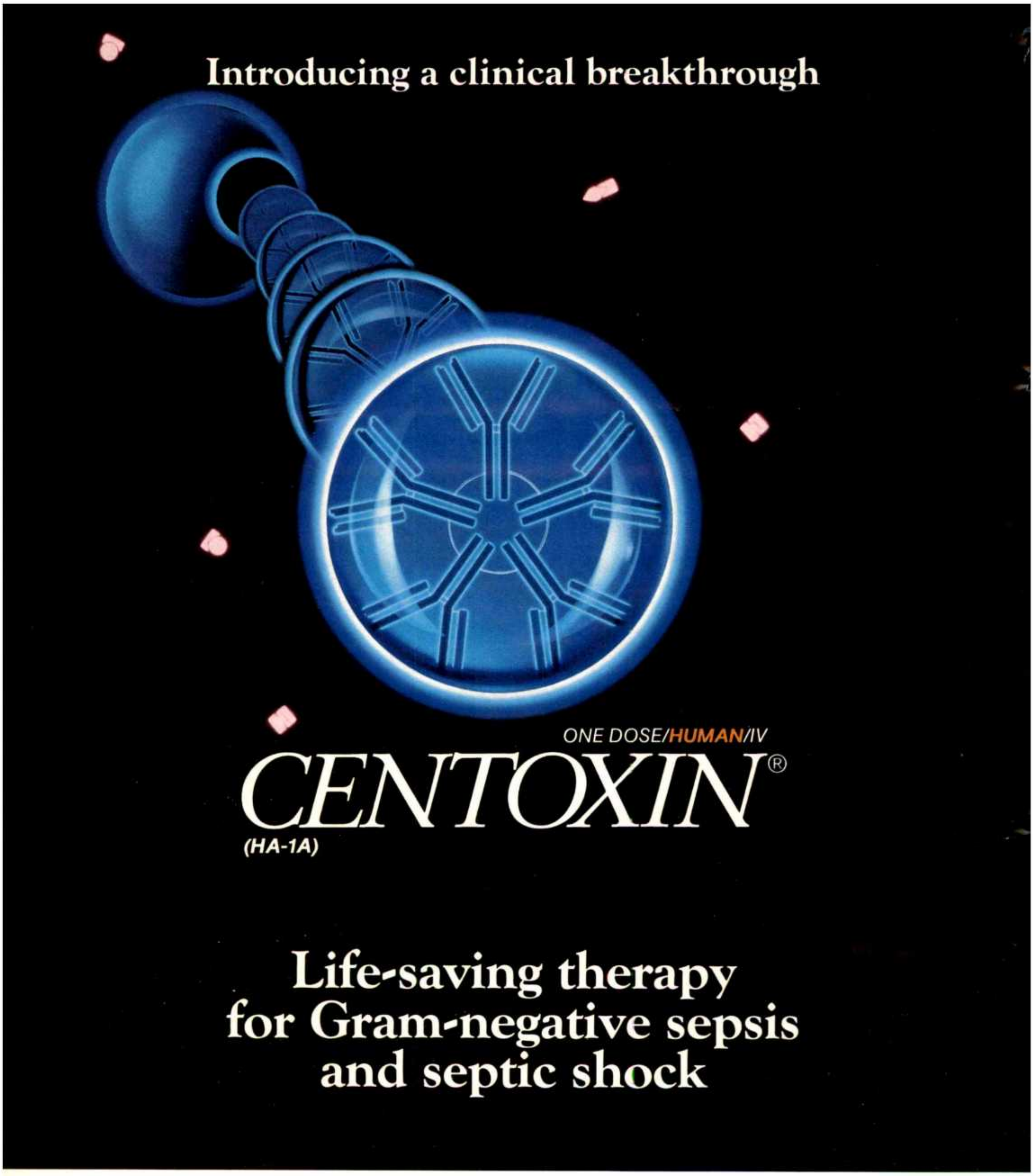
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Volume 78 Number 8 August 1991

LEADING ARTICLES

Justifying arterial reconstruction to crural vessels – even with a prosthetic graft 897
J. H. N. Wolfe and M. R. Tyrrell
Management of idiopathic megarectum and megacolon 899
M. A. Kamm and G. Stabile

REVIEWS

Therapeutic aspects of radio-isotopes in hepatobiliary malignancy 901
J. R. Novell, A. Hilson and K. E. F. Hobbs
Gynaecomastia 907
L. J. Hands and M. J. Greenall

ORIGINAL ARTICLES

Limitations of surgery in the treatment of retroperitoneal sarcoma 912
J.-C. Alvarenga, A. B. S. Ball, C. Fisher, I. Fryatt, L. Jones and J. Meirion Thomas
Tropic role of enteroglucagon in pancreatic adaptation to subtotal enterectomy 917
P. Watanapa, K. Beardshall, J. Calam and R. C. N. Williamson
Clinical and functional results of abdominal rectopexy for complete rectal prolapse 921
J. L. McCue and J. P. S. Thomson
Emergency laparotomy in patients with AIDS 924
T. Davidson, T. G. Allen-Mersh, A. J. G. Miles, B. Gazzard, C. Wastell, M. Vipond, A. Stotter, R. F. Miller, N. R. Fieldman and W. W. Slack
Healing of abdominal incisional hernia in infant rats 927
S. Tsui and H. Ellis
Histopathological evaluation of oesophageal carcinoma: the significance of venous invasion 930
P. H. M. H. Theunissen, F. Borchard and D. C. J. Poortvliet
The sphinctometer: a new device for measurement of lower oesophageal sphincter function 933
D C. Gotley, C. P. Barham, R. Miller, R. Arnold and D. Alderson
Outcome of stapled revision of retracted ileostomy (short note) 935
C. T. M. Speakman, M. C. Parker and J. M. A. Northover
Oxygenation in the stomach and the effect of truncal vagotomy 937
W. G. Sheridan, R. H. Lowndes, M. H. Lewis and H. L. Young
Recurrent peptic ulceration after highly selective vagotomy: long-term outcome 940
G. J. Maddern, J.-N. Vauthey, P. Devitt, R. Britten-Jones, D. J. Hetzel and G. G. Jamieson
The modified AFP score: an attempt to make the results of anti-reflux surgery comparable 942
H. Feussner, A. Petri, S. Walker, E. Bollschweiler and J. R. Siewert
Endoscopic balloon tamponade of iatrogenic bleeding from oesophageal varices (surgical workshop) 946
T. S. Burge, A. J. Russell and M. Rees
Laparoscopic ligamentum teres (round ligament) cardiopexy 947
L. K. Nathanson, S. Shimi and A. Cuschieri
Gastrointestinal mucormycosis 952
S. R. Thomson, P. G. Bade, M. Taams and V. Chrystal
Chemotherapy and surgery for locally advanced cancer of the cardia and fundus: phase II study with methotrexate and 5-fluorouracil 955
J. Th. Plukker, N. H. Mulder, D. Th. Sleijfer, J. Grond and R. C. J. Verschueren
Percutaneous flexible choledochoscopy: a simple method for retained common bile duct stone removal 959
D. Menzies and R. W. Motson

Gallbladder sepsis after stent insertion for bile duct obstruction: management by percutaneous cholecystostomy 961
C. C. Ainley, S. J. Williams, A. C. Smith, A. R. W. Hatfield, R. C. G. Russell and W. R. Lees

Influence of cholecystectomy on symptoms 964
T. Bates, S. R. Ebbs, M. Harrison and R. P. A'Hern

Non-operative management of blunt liver injuries 968
M. J. Hollands and J. M. Little

Mediastinal transfixion with a crossbow bolt (case report) 972
F. J. Mullan, H. O. J. O'Kane, H. K. Dasmahapatra, R. B. Fisher and J. R. P. Gibbons

Accurate intraoperative transhepatic U tube placement 974
J. E. J. Krige, S. J. Beningfield and J. Terblanche

Distal pancreatectomy with and without splenectomy 976
M. C. Aldridge and R. C. N. Williamson

Tumours of the liver, bile ducts, pancreas and duodenum in a single patient with familial adenomatous polyposis (case report) 979
A. D. Spigelman, K. C. R. Farmer, M. James, P. I. Richman and R. K. S. Phillips

Pancreatic pseudocysts: a proposed classification and its management implications 981
A. D'Egidio and M. Schein

Controlled trial of polyglycolic acid versus catgut and nylon for appendicectomy wound closure 985
L. A. Wetter, M. D. Dinneen, M. D. Levitt and R. W. Motson

Randomized trial of intra-arterial recombinant tissue plasminogen activator, intravenous recombinant tissue plasminogen activator and intra-arterial streptokinase in peripheral arterial thrombolysis 988
D. C. Berridge, R. H. S. Gregson, B. R. Hopkinson and G. S. Makin

Infra-inguinal aneurysms: outcome for patient and limb 996
L. J. Hands and J. Collin

Observed incidence of paraplegia after infrarenal aortic aneurysm repair 999
L. J. Hands, J. Collin and P. Lamont

Comparison of iliofemoral and femorofemoral crossover bypass in the treatment of unilateral iliac arterial occlusive disease 1001
M. Hanafy and G. A. McLoughlin

Value of duplex scanning compared with angiography and pressure measurement in the assessment of aortoiliac arterial lesions 1003
D. A. Legemate, C. Teeuwen, H. Hoeneveld and B. C. Eikelboom

Fibrinolytic activity and calf pump failure 1009
H. Gajraj and N. L. Browse

Cervical spine injuries in patients with head injuries 1013
E. Soicher and D. Demetriades

A new instrument: the toothed cutting forceps (surgical workshop) 1014
W. J. B. Smellie

Pylorus-preserving 'cluster' operation 1015
B. Launois and G. G. Jamieson

New prosthetic venous collar anastomotic technique: combining the best of other procedures (surgical workshop) 1016
M. R. Tyrrell and J. H. N. Wolfe)

The British Journal of Surgery – facts and figures 1018
R. C. G. Russell and B. Theis

CORRESPONDENCE 1019

BOOK REVIEWS 1021

NOTICES AND ANNOUNCEMENTS 1023

AMERICAN JOURNAL OF SURGERY CONTENTS 1024

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Br. J. Surg. 1991, Vol. 78, February, 129–130

Mucosectomy in restorative proctocolectomy

In the past decade restorative proctocolectomy has become established as the surgical treatment of choice for ulcerative colitis and most cases of familial adenomatous polyposis[1]. The operation is based on the principle that ulcerative colitis and familial adenomatous polyposis are mucosal diseases and may be cured by excision of all affected mucosa. By combining colectomy with anorectal mucosectomy, a cuff of rectal muscle and the anal sphincters are preserved, while diseased mucosa proximal to the dentate line is removed.

Anorectal mucosectomy carries a risk of injury to the anal sphincters either directly or indirectly during excessive retraction[2]. Injury to the anal sphincter mechanism can be avoided by performing a rectal mucosectomy from above and constructing the ileoanal anastomosis at the top of the anal canal rather than at the dentate line[3]. Using this technique, approximately 1 cm of proximal anal canal mucosa is preserved. The mucosa in this portion of the anal canal differs from the mucosa below the dentate line and the rectal mucosa above the columns of Morgagni. Derived from the cloaca, this transitional zone mucosa is composed of cuboidal not columnar epithelium. In ulcerative colitis, it may not be subject to the same degree of inflammation as the more proximal rectal mucosa. When inflammation is present it may represent a secondary phenomenon similar to backwash ileitis which usually resolves after excision of the diseased colon and rectum. The mucosa in this transitional zone is well supplied with sensory nerve endings which may be important for the maintenance of nocturnal continence.

At operation it is difficult to identify the upper limit of the transitional zone. No more than 1 cm of mucosa above the dentate line should be preserved as to do so may result in recurrence of ulcerative proctitis at the anastomosis[3]. Recently introduced stapling techniques for ileoanal anastomosis have the advantage of making rectal mucosectomy unnecessary. To ensure that all rectal mucosa is excised, the rectum should be cross-clamped at the proposed level of transection, and the distance above the dentate line measured accurately prior to cross-stapling[4]. As circular stapling devices remove a distal doughnut 1·0 cm in diameter, the clamp should lie 4·0 cm from the anal verge. On occasion, particularly in a narrow male pelvis, it may not be possible to cross-staple low enough to excise all rectal mucosa. In such cases rectal mucosectomy and sutured anastomosis at the top of the anal canal should be performed.

The argument in favour of avoiding anorectal mucosectomy does not rest only on technical ease and the saving of operative time. Postoperative functional results are better if it is avoided. Resting anal canal pressure is lower after mucosectomy than after stapled anastomosis without mucosectomy. Anal sensation and discriminatory function are significantly better after end-to-end ileoanal anastomosis (preserving the proximal anal mucosa) than after mucosectomy with endoanal anastomosis[5]. These findings are reflected in improved continence, particularly at night, when minor soiling troubles up to 40 per cent of patients after conventional mucosectomy and ileoanal anastomosis.

The apparent advantages of avoiding anorectal mucosectomy must be balanced against possible long-term risks of preserving potentially diseased mucosa in the distal rectum and proximal anal canal. Two recent studies challenge the safety of preserving the anal transition zone[6,7]. In both studies, histological examination of the transitional zone in anorectal mucosectomy specimens revealed marked features of ulcerative colitis, including dysplasia. One previously unsuspected adenocarcinoma was identified[6]. Both studies concluded that anorectal mucosectomy should be performed in all cases of ileoanal anastomosis for ulcerative colitis. However, recent data from St. Mark's Hospital are more reassuring[8]. Dysplasia of anorectal mucosa was found in only 2·5 per cent of 118 mucosectomy specimens in patients with ulcerative colitis who underwent restorative proctocolectomy. Dysplasia was only found when it was also widespread within the colon and rectum. The study concluded that, in the absence of widespread mucosal dysplasia, the anal transitional zone could

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safely be preserved in ulcerative colitis. This was not the case in familial adenomatous polyposis. In 14 patients with polyposis who underwent restorative proctocolectomy, dysplasia was found in 12 anorectal mucosectomy specimens, demonstrating the clear need for anorectal mucosectomy in all patients with familial adenomatous polyposis.

The presence of severe dysplasia in the rectal mucosa is a cause of concern irrespective of the site of anastomosis and whether or not anorectal mucosectomy is performed. Islets of mucosa may remain on the anorectal muscular cuff despite seemingly complete mucosectomy[9]. Adenocarcinoma has been reported in the rectal cuff of a patient four years after restorative proctocolectomy with anorectal mucosectomy[10]. Severe dysplasia had been present in the anorectal mucosectomy specimen at the time of operation. This report clearly shows that careful histological examination of the excised rectal mucosa is important. If dysplasia is found, excision of any residual, at risk, anorectal mucosa must be considered, even at the price of a permanent ileostomy.

The principle of restorative proctocolectomy is established and refinements of surgical technique will continue. Anal mucosectomy should be always performed in cases of familial adenomatous polyposis. On balance, in ulcerative colitis, the data support the contention that in the absence of rectal dysplasia it is safe to preserve the mucosa of the proximal anal canal. In this situation, the arguments in favour of a stapled ileoanal anastomosis without mucosectomy are persuasive.

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Br. J. Surg. 1991, Vol. 78, February, 131–132

Laparoscopic cholecystectomy

For many years, laparoscopy has been something of a Cinderella in general surgery, advocated by only a small band of devotees, notably as a means of assessment of spread in patients being considered for radical cancer surgery. Indeed, in the minds of many surgeons, laparoscopy came to be associated with the risks of bowel injury during its use in gynaecology and as a rare but real cause of major vascular injury during unskilled insertion of the instrument. All of this now seems destined to change Although only introduced three years ago, laparoscopic cholecystectomy seems to have caught the imagination of the surgical community and, in the course of the last twelve months, we appear to have moved from a position of widespread scepticism to the point where instrument makers are unable to keep pace with surgical demand. While many surgeons may resent the need to learn 'new tricks', all will be relieved by the prospect of gallbladder disease returning to its true surgical home and away from the threat posed by techniques such as chemical stone dissolution and extracorporeal shock wave lithotripsy. All will agree that a minimally invasive technique which safely removes the diseased gallbladder, as well as its contained stones, seems likely to find widespread use.

Cuschieri is one of the small band of surgeons who have remained loyal to the laparoscope over the years[1] and it is no surprise that he and his group have been at the forefront of the development of laparoscopic cholecystectomy. In this issue of the journal (p. 155), the Dundee group describe the results obtained in their first 61 patients. Open cholecystectomy was needed in only one case (because of the demonstration of multiple stones in a dilated common bile duct at operative cholangiography), morbidity was minimal, and the median duration of the procedure was 135 min. Such excellent results are in keeping with those now emerging from other European and North American centres and there is broad agreement that any increase in operation time is outweighed by the reduced metabolic response to surgery and reduced hospital stay (which averaged just under three days in the Dundee study) However, encouraging though these early results are, caution must still be exercised. The Dundee results were not achieved without painstaking ground-work and laparoscopic skills acquired over many years. Patient welfare must not be jeopardized by others attempting laparoscopic cholecystectomy without appropriate training and measured, careful progress up the learning curve. It is already apparent that 'experts' are beginning to abound and the dangers of the 'see one, do one, teach one' philosophy were never more in need of emphasis. There is a pressing need to identify teaching centres where formal training courses will be freely available to those wishing to acquire these new skills.

Given that laparoscopic cholecystectomy seems destined to replace open cholecystectomy in large degree, a number of important issues need to be addressed. As is the case with open cholecystectomy, debate will certainly surround the need for routine operative cholangiography, the use of peritoneal drains and the need for antibiotics. The diminution in the metabolic response to injury merits further study, the optimal method of relieving pain after surgery needs definition, and we must resist the temptation to discharge patients on the first or second postoperative day simply to convince hospital managers of the financial arguments in favour of the laparoscopic approach. The strategy for dealing with choledocholithiasis will have to be defined and the arguments for and against the use of lasers in dissection will have to be resolved on the basis of objective study rather than on opinion often influenced by their availability to the unit concerned. Although the view obtained during laparoscopic cholecystectomy may be superior to that during open operation and while obesity is not in itself a contraindication, non-functioning fibrotic gallbladders took longer to remove in the Dundee study than functioning gallbladders Significantly, all of the procedures reported from Dundee were undertaken on an elective basis and the role of the laparoscopic technique in removing an acutely inflamed gallbladder awaits definition As in open operation, careful display of the structures in Calot's triangle is the key to avoiding injury to the common hepatic duct or common bile duct. Injury to the duct system is already a recognized complication of the laparoscopic technique and, as in conventional cholecystectomy, young thin patients with small calibre duct systems may be at particular risk[2] from inadvertent clipping and division of the common bile duct instead of the cystic duct In our view, the need to avoid or at least recognize bile duct injury may be just as

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important an indication for operative cholangiography as the need to detect choledocholithiasis.

As in so many areas of the crumbling land mass of general surgery, increasing specialization raises important implications for training. Should all consultant general surgeons wishing to practice biliary surgery acquire the skills needed for laparoscopic cholecystectomy? Clearly not all will wish to do so, and those in sight of retirement may well elect to canter gratefully to the finish line without feeling the need to retrain. Should all general surgical trainees acquire these skills? In our view, the answer is a cautious yes. It seems certain that minimally invasive techniques are here to stay and will find increasing application; in its turn, laparoscopy may well come to occupy a more important role in both diagnosis and management[3,4]. Given the continued high incidence of symptomatic gallstone disease, widespread adoption of laparoscopic cholecystectomy as the technique of choice would have implications for surgeons in district general hospitals and teaching hospitals alike. In the district general hospital context, one can envisage a situation where say one of four consultant general surgeons might develop particular skills in laparoscopy, combined perhaps with skills in interventional endoscopy. In the teaching hospitals, specialist hepatobiliary-pancreatic units are already developed and, in addition to undertaking complex major surgical procedures, such units could readily provide training in laparoscopic techniques for future generations of surgical trainees. As in peptic ulcer surgery where the development of alternative methods of management has resulted in real concern regarding a lack of trainee experience in vagotomy and drainage operations, let alone partial gastrectomy, so we will have to come to terms with the problem of lack of trainee experience in conventional biliary surgery in the years to come.

In a further paper in this issue, Troidl *et al.* (p. 150) discuss the arguments for and against a prospective controlled comparison of laparoscopic *versus* open cholecystectomy. In the ideal world such a trial would indeed be desirable. However, given the impressive early results of laparoscopic cholecystectomy, coupled with an increasing awareness of its potential by patients and general practitioners, such a comparison may now be impossible to mount. If we are to move to widespread implementation of laparoscopic cholecystectomy without controlled study, meticulous audit of results will be of paramount importance. We must not squander the potential of this exciting new approach by ill-judged and hasty application of the technique by ill-trained surgeons. We must not forget that the optimal method of managment of gallstone disease will not rest on rigid unthinking devotion to any one technique but on judicious selection of the most appropriate method or combination of methods for the individual circumstances.

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Review

Br. J. Surg. 1991, Vol. 78, February, 133–137

Surgical strategies in the treatment of pancreatic necrosis and infection

Controversy still surrounds the management of necrotic and septic complications of acute pancreatitis. A review of the literature of the past decade dealing with the surgical treatment of pancreatic necrosis, pancreatic abscess and infected pancreatic necrosis has been undertaken. Three main patterns of management could be identified: (1) 'conventional treatment', consisting of pancreatic resection or necrosectomy with drainage; (2) 'local lavage', consisting of necrosectomy followed by regional lavage; and (3) 'open management', with resection or necrosectomy followed by planned multiple re-explorations. From this review it appears that local lavage and open management offer better survival prospects than conventional treatment. Open abdomen techniques, however, are associated with an increased risk of complications, such as colonic necrosis, intestinal fistula, and intra-abdominal bleeding. Excellent results can be achieved in specialized centres with any of the three methods, provided adequate debridement and prompt reoperations are undertaken if the septic state persists.

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Pancreatic necrosis and sepsis are the leading causes of mortality in acute pancreatitis. Although aggressive organ-system support has resulted in improved survival in the early stage of the disease, patients continue to die at a later stage from necrotic and septic complications culminating in multiorgan failure[1]. The reported mortality rate of these complications ranges from 5 to 80 per cent[2,3]. Such variability is partly related to the fact that septic complications of acute pancreatitis do not constitute a homogeneous disease; instead, they comprise a wide spectrum of conditions including pancreatic abscess, infected pancreatic necrosis, infected pseudocyst and peripancreatic necrosis, all of which carry variable mortality rates[1].

The severe forms of acute pancreatitis are uncommon, occurring in approximately 5 to 15 per cent of patients with acute pancreatic inflammation[2,4]. A single surgeon or centre is unlikely, therefore, to acquire a large experience with the treatment of these conditions. Consequently, most available reports are retrospective and uncontrolled, contain a limited number of cases, and include patients suffering from the wide variety of conditions mentioned above.

During the 1980s, three main patterns of management could be identified in the surgical management of necrotic and infective complications of acute pancreatitis. (1) 'Conventional' treatment, including resection of the involved pancreatic tissue or necrosectomy, followed by drainage. Reoperations are performed 'on demand', as dictated by the appearance of clinical or radiological evidence of residual necrosis or infection. (2) 'Lavage' treatment in which necrosectomy is followed by local irrigation or lavage of the involved retroperitoneal area. (3) The 'open management' approach, involving resection or necrosectomy followed by various combinations of planned and staged re-explorations. These are undertaken irrespective of the patient's general condition and stop only when the peritoneal cavity is deemed to be clean.

In this review, an attempt is made to evaluate the results of these approaches.

Methods

We reviewed the English literature during the 1980s dealing with the surgical treatment of pancreatic abscess, pancreatic necrosis or infected pancreatic necrosis (as defined by Frey *et al.*[1]). Only reports of patients treated during the past 15 years were included. Patients with infected pseudocysts and localized postoperative pancreatic abscess were excluded. In all 920 cases satisfied these criteria and were analysed to compare mortality and complication rates.

The treatment methods were divided into the three groups mentioned above.

Group 1 'Conventional treatment': resection or necrosectomy and drainage with re-explorations 'on demand' ($n=516$)[3–19].
Group 2 Necrosectomy followed by local lavage ($n=216$)[2,12,16,20–24].
Group 3 'Open management': resection or necrosectomy followed by scheduled re-laparotomies and open abdominal management ($n=188$)[25–34].

Tables 1–3 show the series reviewed in each group.

Statistical analysis was performed using Fisher's exact test

Results

Mortality

The overall mortality rate in the three groups was 36 per cent, 23 per cent and 25 per cent, respectively. An attempt was then made to produce more 'homogeneous groups' by excluding patients with localized lesser sac abscesses and those with a fulminating course who succumbed early (e.g. within the first week) after admission. In a few series, some patients were thus excluded; the entire series was excluded if such patients could not be identified. Such excluded patients or series are identified in *Tables 1–3* by an asterisk. The mortality rate in the 'homogeneous groups' was 40 per cent, 17·5 per cent and

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Table 1 *Group 1 outcome in patients treated by resection or necrosectomy with drainage*

Reference	No of cases	No of deaths
Allardyce[3]	17	14
Wilson *et al.*[4]	14	4
	7 (Pancreatic resection)	4
Smadja and Bismuth[5]*	38	16
Warshaw and Jin[6]	45	11
Ranson[7]	29	5
Stricker and Hunt[8]	22	9
Alexandre and Guerrieri[9]*	27	9
	25 (Pancreatic resection)	16
Nordback *et al.*[10]	37 (Pancreatic resection)	16
Malangoni *et al.*[11]	27	9
Teerenhovi *et al*[12]	12	2
Crass *et al.*[13]	21	4
McClave *et al.*[14]*	21	7
Teerenhovi *et al.*[15]	84 (Pancreatic resection)	38
Kivilaakso *et al*[16]*	18 (Pancreatic resection)	4
Aranha *et al*[17]*	20	6
Nordback and Auvinen[18]	40 (Pancreatic resection)	11
Donahue *et al.*[19]*	12	1
Total		
Overall	516	186 (36·0%)
Resections excluded	305	89 (29·2%)

* Excluded in more homogeneous series (see text)

Table 2 *Group 2. outcome in patients treated by necrosectomy with local lavage*

Reference	No of cases	No. of deaths
Larvin *et al.*[20]	14	3
Beger *et al*[2]	95	8
Teerenhovi *et al.*[12]	12	4
Nicholson *et al.*[21]	11	3
Shi *et al.*[22]*	34	12
D'Egidio[23]	6	2
Kivilaakso *et al*[16]*	17	8
Gebhardt and Gall[24]	27	9
Total	216	49 (22·7%)

* Excluded in more homogeneous series (see text)

22 per cent, respectively ($P<0·05$ between group 1 and groups 2 and 3; $P>0·05$ between group 2 and group 3). Analysis of only those patients with infected pancreatic necrosis documented by bacteriology/Gram stain, showed a statistically significant difference ($P<0·05$) in mortality rate between group 1 (42 per cent), group 2 (18 per cent), and group 3 (21 per cent) (*Table 4*). There was no significant difference between group 2 and group 3 in terms of mortality rate.

Complications

Table 5 shows the incidence of intra-abdominal haemorrhage, pancreatic fistula and intestinal complications in the three treatment groups. Intestinal complications appeared to be commoner in group 3.

Reoperations

Thirty-six per cent of the patients in group 1 and 33 per cent in group 2 required reoperation, usually because of persistent intra-abdominal sepsis. Most patients in group 3 underwent 'planned' re-explorations as a part of the aggressive policy of reoperation.

Discussion

Uncertainties still surround the correct management of necrotic and septic complications of acute pancreatitis, particularly with regard to the timing and method of surgical intervention. Until recently, the debate has been compounded by the lack of an accurate terminology to define these disease processes.

Pancreatic abscess and infective pancreatic necrosis constitute two different entities in the spectrum of septic complications of acute pancreatitis[1]. Pancreatic abscess consists of a walled-off collection of purulent material within or in the vicinity of the pancreas, and results from liquefaction of areas of necrosis or secondary infection of an acute pseudocyst. It often occurs at a relatively late phase once the acute

Table 3 *Group 3· outcome in patients treated by resection or necrosectomy with 'open management'*

Reference	No of cases	No. of deaths
Wertheimer and Norris[25]	10	2
Bradley[26]	28	3
Stone *et al.*[27]	22	2
	14*	5
Garcia-Sabrido *et al.*[28]	38	8
	11*	1
Walsh *et al*[29]	8	4
Schein[30]	9	5
Pemberton *et al*[31]	16	3
Aldridge *et al*[32]	15*	5
Mastboom *et al*[33]	6	3
Mughal *et al.*[34]	11*	5
Total	188	46 (24·5%)

* Excluded in more homogeneous series (see text)

Table 4 *Mortality in patients with documented infective pancreatic necrosis*

Reference	No of cases	No of deaths
Group 1		
Wilson *et al*[4]	14	7
Allardyce[3]	17	14
Warshaw and Jin[6]	45	11
Total	76	32 (42%)
Group 2		
Beger *et al*[2]	37	5
Larvin *et al*[20]	14	3
Nicholson *et al.*[21]	11	3
Total	62	11 (18%)
Group 3		
Bradley[26]	28	3
Stone *et al.*[27]	22	2
Wertheimer and Norris[25]	10	2
Garcia-Sabrido *et al.*[28]	23	7
Schein[30]	9	5
Total	92	19 (21%)

Table 5 *Incidence of local complications in different groups**

	Group 1 ($n=256$) (%)	Group 2 ($n=166$) (%)	Group 3 ($n=134$) (%)
Small bowel complication	5	4	14
Colonic complication	8	2	13
Haemorrhage	14	8	16
Pancreatic fistula	16	17	17

* Groups including only series with reported complications

inflammatory process has subsided and is associated, therefore, with a relatively good prognosis[35]. Infective pancreatic necrosis represents an infection of devitalized pancreatic and/or peripancreatic tissue; it occurs at an earlier stage of the disease and is associated with a worse prognosis[1,35]. The systemic repercussions, often culminating in the failure of one or more organ-systems, are probably related to release from the necrotic tissues of toxins and vasoactive substances such as endotoxin, trypsin and phospholipase[36]. The production of such substances is dependent on the extent of necrosis and degree of bacterial contamination[37]. Recently, there has been a substantial improvement in the early diagnosis of pancreatic necrosis and its superinfection given that contrast-enhanced computed tomography has emerged as a reliable means of visualizing the presence of necrosis[38–41].

Two main factors should influence the correct timing of operation in patients with pancreatic necrosis, namely the severity of illness and the presence or absence of infection. In patients with sterile pancreatic necrosis, early surgical intervention may be associated with a risk of infection and increased mortality[3,20,24,40]. However, it is necessary to distinguish between stable patients and those who are severely ill or rapidly deteriorating. Failure to improve or deterioration in the first 48–72 hours, appear to be the most common indications for early surgical intervention[2,4]. Although a few studies have found a correlation between delayed surgery and fatal outcome in this group of patients[4,10], others have not[5,11]. Delaying debridement until the second or third week appears a more attractive option[4,8,24], as deferred operation may allow further demarcation of the necrotic tissues, improving intraoperative identification of necrotic material and its removal[21,42]. Conversely, delayed surgery in the presence of infected pancreatic necrosis is associated with persisting sepsis and higher fatality rates[4,11,13]. Bacteriological studies of necrotic material aspirated percutaneously under sonographic or computed tomographic guidance have been shown to allow accurate early diagnosis of infected necrosis[13,43–45].

Once the presence of infected pancreatic necrosis has been established, the surgeon's task is first to remove the necrotic infected material,, second, to evaluate toxic intraperitoneal products, third, to deal effectively with re-accumulating slough and infection, and finally, to avoid damage to adjacent healthy abdominal structures.

In this collective review, we have attempted to compare the efficacy of the three current surgical approaches to these tasks. The inherent pitfalls of such a review which analyses patients with complex disease processes dealt with a variety of ways are obvious. Nevertheless, our effort to stratify these patients into reasonably uniform disease categories and treatment methods allows the following observations.

'Conventional treatment'

The mortality rate in the group 1 patients was 36 per cent (range 8–82 per cent) However, if patients with formal pancreatectomy are excluded, the mortality rate drops to 29 per cent (*Table 1*) When only patients with documented infected pancreatic necrosis were considered, the mortality rate was 42 per cent (range 24–82 per cent) (*Table 4*).

Reoperations, usually for persistent intra-abdominal infection, were necessary in more than one-third of these patients. Recently, excellent results have been achieved with such conventional methods in a few centres[6,7,13]. These improvements are ascribed to improved imaging techniques, earlier diagnosis, aggressive debridement and wider drainage. The use of a long subcostal or midline incision is equally distributed among authors, as is the use of a transmesocolic or transgastrocolic approach to the lesser sac. The extent and completeness of debridement has been found to play a significant role in the survival of these patients[3,6,8]. For example, Stricker and Hunt[8] reported a 54 per cent mortality rate for patients treated by limited exploration, compared with 22 per cent for those having wide exploration. Various combinations of soft rubber drains and sump drains have been used, and wide drainage with multiple drains was found to improve survival in two studies[8,11].

'Local lavage'

Local irrigation of the pancreatic bed, following necrosectomy, has gained popularity in recent years. Proponents of this technique claim that the combination of necrosectomy and postoperative local lavage allows atraumatic and continuous removal of devitalized tissues, as well as elimination of organisms and biologically active compounds[2,20,21,36,46] However, inadequate debridement may lead to failure of this technique[22]

The drains are often specially made and should have a double lumen with a large diameter (20 mm). Two drains appear to be adequate The gastrocolic and duodenocolic ligaments should be closed to avoid dispersion of irrigating fluid into the entire abdominal cavity. The average amount of fluid used is approximately 6 litres a day (range 2–20 litres), the amount depending on the extent of necrosis. Lavage is stopped when there are no signs of active pancreatitis (low level of isoamylase and trypsin in the fluid), the effluent is clear, or sinography shows that the cavity has been obliterated[2,20,21]. The overall mortality rate in group 2 patients was 22·7 per cent (range 8–47 per cent) (*Table 2*). When only patients with documented infective pancreatic necrosis were considered the mortality rate was 18 per cent (range 14–27 per cent). Reoperations were necessary in one-third of these patients.

Recently, two controlled randomized studies failed to demonstrate any advantage of postoperative local lavage over conventional methods[12,16]. However, in one study[16] lavage was compared with pancreatic resection and in the other[12] inadequate information is provided regarding the extent of debridement. Furthermore, both studies involved a small number of patients. In the past, enthusiasm for non-operative peritoneal lavage in acute pancreatitis[47] subsided when well-designed controlled studies showed no benefit[48,49], but this may not apply to the use of lavage following necrosectomy. The incidence of intestinal and haemorrhagic complications in this group appears to be relatively low (*Table 5*).

'Open management'

Frustration with the conventional surgical approach and the assumption that pancreatic sepsis cannot be controlled adequately by a single surgical procedure have led some surgeons to adopt an aggressive operative approach involving open packing and frequent, multiple re-laparotomies[26] After debridement has been performed, the septic area is packed with gauze and the abdomen left open. The packs can be changed daily under sedation in the intensive care unit. The use of a porous non-adherent petrolatum gauze in the base of the cavity, and around exposed vessels, has been advocated by Bradley as a way of decreasing injury to the surrounding structures[26]. Other authors have avoided packing and used a synthetic mesh or a zip in the abdominal fascia or skin to allow easy re-entry for repeated lavage[28,29]. The overall mortality rate in group 3 patients was 24·5 per cent (range 11–55 per cent) (*Table 3*) and it was 21 per cent (range 11–55 per cent) in patients with documented infected pancreatic necrosis (*Table 4*). However, the schedule of repeated debridement and open packing caused a significant number of local complications in this group (*Table 5*) and colonic necrosis or fistulae developed in 13 per cent of patients The pathogenesis proposed by most authors is ischaemia caused by the extension of the necrotizing process into the mesocolon[50–53]. However, the high incidence of colonic complications in this group suggests an iatrogenic aetiology, in which aggressive debridement of necrotic mesocolic fat, injury to the bowel during abdominal re-entry, and pressure from adjacent packs and the overlying synthetic mesh are causative[30]. Similar factors are probably responsible for the high incidence of small bowel fistulae in this group[30,33,54]. Massive haemorrhage from the pancreatic bed

P 25 338.

was also common in group 3. Damage to the splenic vessels during the change of packing or from exposure injury may be the responsible factors[30].

What then is the surgical approach of choice in managing necrotic and septic complications of acute pancreatitis? Overall, this collective review shows that necrosectomy supplemented by local lavage or the open method are associated with improved survival over that achieved with conventional treatment. The open method, however, carries a higher morbidity rate than local lavage.

Closer examination of the individual series may offer a different perspective in that the results obtained in specialized centres committed to the treatment of complicated acute pancreatitis are excellent, irrespective of the surgical approach. Thus the mortality rates reported by Warshaw and Jin in the last 5 years of their study[6] using the conventional approach, by Beger *et al.*[2], practising local lavage, and by Bradley[26] recommending open packing and planned re-debridement, were 5 per cent, 8 per cent and 11 per cent, respectively. Furthermore, if Beger's large series[2] is excluded, the mortality rate in the more homogeneous series of local lavage would rise to 30 per cent, a figure comparable to that achieved by most series using conventional treatment. In addition, a wide range of results has been achieved with the various approaches. For example, while some authors managed to obtain a low mortality rate with open methods[25–28,31], others using similar methods did not[29,30,32,34]. Differences in the severity of illness of the patients or in the facilities and surgical skills available in the various centres could be implicated. Another factor which could play a role is the age of the patients treated, but no significant differences were found in average age among the three groups (48 years in group 1, 49·2 years in group 2, and 49·3 years in group 3). While some series showed that age was correlated with fatal outcome[3,20], others did not[11,21]. Differentiation between peripancreatic and parenchymal necrosis is also important in the analysis of the results; two studies showed a mortality rate of less than 25 per cent in patients with peripancreatic necrosis, whereas a mortality rate greater than 50 per cent was noted in patients with pancreatic necrosis[4,15]. Unfortunately, very few studies differentiate between these two entities.

We conclude that the cornerstone for improved survival in patients with necrotic and infected pancreatitis is adequate debridement combined with modern intensive support of the patient. This can be achieved with any of the three approaches considered, provided that all slough and septic collections are removed and that the patients are re-explored promptly if the septic state persists. However, we believe that rigid adherence to one of the three policies should not be practised; rather we suggest that the surgical approach should be tailored to the individual operative findings and clinical course. Only large-scale randomized prospective studies with clear stratification of patients will further clarify this debate.

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Merkel cell tumour: clinical behaviour and treatment

We have reviewed 30 reports of Merkel cell tumour and described a further five cases in order to establish a database and from this more clearly define the biology of this tumour, prognostic factors that govern outcome, and optimal management. After excision alone of the primary lesion, local recurrence occurred in 39 per cent of patients and regional failure occurred in 46 per cent. In contrast, in patients treated by excision plus prophylactic treatment (adjuvant node dissection and/or adjuvant radiation), local recurrence occurred in 26 per cent and regional failure in 22 per cent. Locoregional recurrence carried an ominous significance with 67 per cent of patients subsequently dying of the disease. For patients who either presented with regional disease or later developed regional disease, the best outcome (44 per cent survival with mean follow-up of 40 months) was obtained following treatment by therapeutic node dissection with or without radiation. In contrast, treatment of regional disease with radiation alone was associated with only a 20 per cent survival rate. Unfavourable prognostic factors included young age, lesions sited in the head and neck or trunk, male sex, and the presence of locoregional failure and/or systemic disease. We conclude that Merkel cell tumours behave in a similar manner to the aggressive variants of melanoma and that minimal treatment consists of wide surgical resection of the primary lesion (with a margin of 2·5–3 cm) coupled with resection and probably also radiation of regional disease if present. In addition, consideration should be given to prophylactic node dissection in node negative patients, especially in those patients with unfavourable prognostic factors.

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Merkel cell tumour is an unusual neuroendocrine tumour. Typically skin lesions present on the limbs or head and neck, are pink or grey and, because they arise in the dermis rather than the epidermis, rarely ulcerate[1–10]. The histology of Merkel cell tumour is now well described[1–5], and more recently the ultrastructural details have been resolved [10–13]. However, the clinical behaviour of this tumour is not well described, and there is no agreement regarding optimal treatment as the majority of clinical reports concern small numbers of patients; in many of these reports the emphasis has been on pathology and diagnosis rather than treatment.

We have reviewed the details of 234 patients with Merkel cell tumour: five cases of our own and 229 cases reported in 30 papers[1–30]. We have focused our review on clinical presentation and tumour behaviour, and have attempted to define prognostic factors as well as a strategy for treatment.

Patients and methods

We have reviewed the data presented in 30 reported series of patients with Merkel cell tumour[1–30]. This accounted for 293 cases in total but in only 229 cases was there sufficient information available to incorporate into a database We have also reported five new cases, bringing the total to 234 cases (*Table 1*).

Data were collected with particular reference to age, sex and race of patient, mode of presentation, diagnosis, primary management, salvage therapy and outcome. Prognostic factors influencing outcome have been defined and the statistical significance of each factor has been assessed using a χ^2 analysis.

The five patients seen in Auckland had a mean age of 75 years (range 57–87 years) and all but one were women. In two cases the tumour was in the head and neck, and in three cases in the limbs. Three patients had nodal disease at presentation, and one patient had systemic disease. One patient previously had skin cancer and one had dural ectasia. Two patients underwent wide local excision alone and the three who presented with regional disease were treated by wide local excision, therapeutic lymph node dissection and adjuvant radiation. Four of the five patients are alive and well with a mean follow-up of 6 months.

Results

The primary site for tumours in the 234 patients was head and neck (108 patients), leg (77 patients), arm (42 patients) and trunk (seven patients). There were 129 women with a mean age of 70 years (range 23–92 years) and 105 men with a mean age of 68 years (range 23–92 years; see *Table 1*).

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Table 1 *Details of patients with Merkel cell tumours*

Author (year)	Reference	*n*	Mean age	M:F	Head and neck	Trunk	Limbs
Toker (1972)	1	5	70	2:3	2	1	2
Van Dyk and Ten Seldam (1975)	2	1	72	0 1	1	–	–
Tang and Toker (1978)	3	9	61	4:5	2	1	6
Taxy *et al.* (1980)	4	1	74	0·1	1	–	–
De Wolf Peeters *et al.* (1980)	5	5	69	0·5	3	–	2
Sibley *et al* (1980)	6	2	80	1·1	2	–	–
Johannessen and Gould (1980)	7	1	78	0 1	1	–	–
Ecker *et al.* (1982)	8	6	56	1·5	3	–	3
Pilotti *et al.* (1982)	9	10	66	2.8	3	1	6
Warner *et al.* (1983)	10	6	62	3 3	1	2	3
Beyer *et al.* (1933)	11	1	80	0·1	1	–	–
Rustin *et al.* (1983)	12	1	75	0 1	–	–	1
Frigerio *et al.* (1983)	13	15	70	3.12	6	1	8
Goepfert *et al* (1974)	14	29	66	23:6	29	–	–
Pettinato *et al* (1984)	15	1	61	0.1	–	–	1
Sibley *et al.* (1985)	16	43	70	21.22	17	2	24
Schnitt *et al.* (1966)	17	1	60	1·0	–	–	1
O'Rourke and Bell (1986)	18	1	90	0·1	1	–	–
Meland and Jackson (1986)	19	23	63	15:8	10	4	9
Raaf *et al.* (1986)	20	4	68	2.2	–	1	3
Leong and Dixon (1986)	21	13	70	8:5	7	1	5
Cotlar *et al.* (1986)	22	8	67	7:1	5	–	3
O'Rourke and Bourne (1987)	23	3	62	3·0	3	–	–
O'Brien *et al.* (1987)	24	11	72	7·4	8	–	3
Bourne and O'Rourke (1988)	25	13	70	9:4	11	–	2
Tennvall *et al.* (1989)	26	18	70	10:8	9	1	8
Pacella *et al.* (1989)	27	20	65	8 12	15	1	4
Shaw and Rumball (1990)		5	75	1:4	2	–	3
Wick *et al.* 1983	28	13	62	8:5	7	–	6
Kirkham and Isaacson (1983)	29	3	79	1.2	2	–	1
Kroll and Toker (1982)	30	21	69	11:10	9	–	12
Total		293	70	151:141	161	16	116

Stage of disease

Twenty-three patients had regional disease on presentation. Of the 108 patients with head and neck tumours, eight (7 per cent) had nodal disease at presentation, as did five of 42 (12 per cent) patients with arm lesions, and 10 of the 77 (13 per cent) patients with leg lesions. Three patients had systemic disease at presentation, and the remaining 208 had localized disease.

Node negative patients

Initial treatment. There were 208 patients in this group. Wide local excision alone was performed in 181, and in 27 patients surgical treatment of the primary lesion was coupled with prophylactic nodal dissection, nodal radiation, or a combination of the two.

After wide local excision alone, 83 of the 181 patients developed regional failure (46 per cent), and 71 (39 per cent) also developed local recurrence Seventy patients died of the disease (39 per cent), and the 111 surviving patients were followed for an average of 25 months.

In contrast, in the patients who underwent prophylactic node dissection and/or radiation, locoregional recurrence was less common Of the 27 patients, seven (26 per cent) developed local recurrence and six (22 per cent) also developed regional failure. Eight patients (30 per cent) died of the disease and the remaining 19 patients (70 per cent) were alive after a mean follow-up of 40 months (see *Table 2*).

Table 2 *Treatment and outcome in node-negative patients*

	n	Alive	Local failure	Regional failure	Death
Excision alone	181	110 (60)	71 (39)	83 (46)	70 (39)
Excision + adjuvant treatment	27	19 (70)	7 (26)	6 (22)	8 (30)

Values in parentheses are percentages Adjuvant treatment prophylactic node dissection or nodal radiation in addition to excision of primary lesion. Mean follow-up for survivors. 28 months. Mean time from initial treatment until recurrence· 7 months for local recurrence, 12 months for regional recurrence. Mean time between locoregional failure and death: 11 months

Subsequent treatment of delayed regional disease. Three patients did not undergo any treatment, and all died (mean survival 3 months). In addition, six patients were treated with a variety of chemotherapeutic agents either alone or in combination, and all died (mean survival 13 months)

Radiation alone was used in 25 patients. Five (20 per cent) were alive after a mean follow-up of 40 months, and 80 per cent (20 of 25) died of the disease (mean survival 14 months) after developing regional failure.

Fifty-five patients were treated by lymphadenectomy either alone or in combination with adjuvant radiation Thirty-two

Table 3 *Treatment* versus *outcome in node-positive patients*

	n	Alive	Dead
No treatment	4	0	4 (100)
Chemotherapy	7	0	7 (100)
Radiation	30	6 (20)	24 (80)
Node dissection with or without radiation	71	31 (44)	40 (56)

Values in parentheses are percentages. Note. both patients who presented with nodal disease and patients who subsequently developed nodal disease are included

of 55 (58 per cent) died of the disease (mean survival 13 months) after developing regional failure, and 23 of 55 (42 per cent) were alive after a mean follow-up of 54 months.

Significance of local and regional failure. Both local recurrence and regional failure were associated with a high chance of death occurring. Seventy-eight of the 208 patients who were initially node negative died of the disease (38 per cent). Fifty-seven (73 per cent) had previously developed local recurrence, 61 (78 per cent) had previously developed regional failure, and all had metastatic disease

Patients who presented with synchronous or metachronous regional disease

Treatment. Local excision with radiation was used in five of the 23 patients who had regional disease on presentation. Excision of the primary lesion plus lymph node dissection was employed in 11, excision of the primary lesion with node dissection and radiation was performed in five patients, one patient was not treated, and one patient underwent excision of the primary lesion plus chemotherapy.

Overall, 14 patients (61 per cent) died of the disease, with a mean survival time of 17 months. The remaining nine patients were alive after a mean follow-up of 12 months.

Four of the five patients treated by excision plus radiation died of the disease, while seven of 11 (64 per cent) patients treated by excision and node dissection died of the disease. Of the five patients treated by excision, node dissection and radiation, one died at 8 months, and the remaining four were alive after a mean follow-up of 18 months.

Results. The overall influence of individual treatment regimens for patients who either presented with regional disease or subsequently developed regional failure is summarized in *Table 3*.

Treatment of systemic disease

Three patients presented with systemic disease and 81 patients developed systemic disease after initial treatment. The outcome after treatment of systemic disease was poor. Twenty-six patients were not treated and the mean time from development of metastases until death was 4 months. Twenty-seven patients were treated by radiation, 14 with a variety of chemotherapeutic agents, and 17 were treated by both radiation and chemotherapy. The mean times from development of metastases until death were 8 months, 8 months and 6 months respectively.

Prognostic factors

Sex was a prognostic factor in that 47 per cent (49 of 105) of men died *versus* 34 per cent (44 of 129) of women.

Anatomical site also influenced outcome Twenty-nine per cent (35 of 119) of patients with limb lesions died and 45 per cent (52 of 115) of patients with trunk or head and neck lesions died of the disease.

Age was a prognostic factor in that 40 per cent (67 of 166) of patients aged >60 years, 53 per cent (25 of 47) of patients aged 40–60 and 60 per cent (three of five) of patients aged <40 years died of the disease.

Nodal status was also predictive. Seventy-five of the 112 (67 per cent) patients who either presented with nodal disease or subsequently developed regional failure died. In contrast, of the patients who did not develop regional disease, only 27 of 115 (23 per cent) died.

Systemic disease was prognostic as all but one of the 84 patients with systemic disease died of the disease; the remaining patient had a spontaneous remission.

Local recurrence was prognostic given that 57 of 71 patients (80 per cent) who developed local recurrence died of the disease (see *Table 4*).

Discussion

One striking feature of Merkel cell tumour is the similarity of its biology to that of malignant melanoma. This is no surprise as both cancers occur most commonly in the skin, and both are of neural crest origin[1–5]. As treatment regimens for Merkel cell tumour are still evolving, we have attempted to fill some of the gaps in our knowledge by drawing on what is known for melanoma.

The five additional patients we have reported demonstrate some new aspects. One of our patients with a large head and neck tumour was Polynesian and we are unaware of any other cases reported in non-Caucasians. This is consistent with the racial distribution of melanoma. In our review of melanoma in Auckland (the largest Polynesian city) only 1·5 per cent of melanomas occurred in non-Caucasians[31]. Another of our patients had the associate neural crest defect of dural ectasia. This finding, along with the observations of others that: (a) Merkel cell tumour may develop in association with other types of skin cancer of neural crest origin[13,14,22,23,27], (b) that Merkel cell tumours have been associated with calcitonin secretion (calcitonin is normally secreted by the neural-crest derived parathyroid glands), and (c) that there may be an association of some endocrine tumours on the basis of common neural crest origin development (multiple endocrine neoplasia syndromes types 1–3) raises the possibility that there may be an association between Merkel cell tumours and other tumours of neural crest origin

Our review demonstrates that the most common site for the tumour is the head and neck, followed by the limbs, and that the average age of patients at presentation is approximately 70 years, with females predominating. These demographic features differ from those of melanoma in the sense that melanoma, although more common in females, is most commonly seen in the limbs (only 15 per cent of cases occur in the head and neck)[32], and the average age at presentation is younger[31].

Table 4 *Prognostic factors in patients with Merkel cell tumour*

	n	Deaths	χ^2	*P*
Sex				
Male	105	49		
Female	129	44	3·8	<0·05
Site				
Head and neck, trunk	115	52		
Limbs	119	35	7·1	<0·01
Age				
$\leqslant 60$ years	67	37		
>60 years	166	67	5·3	<0·02
Nodes				
Not involved	115	27		
At presentation	23	14	14	<0·001
Delayed	89	61	>20	<0·001
Local failure				
Present	71	57		
Not present	121	35	>20	<0·001
Systemic disease				
Present	84	83		
Not present	150	5	>20	<0·001

The prognostic features of Merkel cell tumour (including the age and sex of the patient, site of the primary lesion, and the presence of local or regional recurrence or systemic disease) can also be compared with equivalent data from melanoma patients. In Merkel cell tumour the outcome for younger patients was less favourable than for older patients, while for melanoma the opposite has been recorded[33]. For Merkel cell tumours the prognosis was less favourable for lesions in the head and neck or trunk than for limb lesions, a finding that parallels the situation in the melanoma[31,34]. As is the case with melanoma, the presence of regional or systemic disease carried an ominous prognosis[32], and there is no effective treatment for systemic disease in either condition. The 5-year survival rate for patients with melanoma with regional disease is approximately 30 per cent[35], and the situation for patients with Merkel cell tumour appears to be similar in that 33 per cent of patients with regional disease were alive after a mean follow-up of 51 months. The outlook for patients with Merkel cell tumour and patients with melanoma with systemic disease also appears to be similar. At present there is no effective chemotherapy regimen for melanoma[36]. Response rates of up to 25 per cent are reported but the majority of patients with systemic melanoma are dead within 6–9 months[36]. The pattern of survival for the patients with Merkel cell tumour who have systemic disease was similar irrespective of whether they were treated with chemotherapy and/or radiation, or managed expectantly.

Overall the outcome for patients with Merkel cell tumour is poor with approximately 35 per cent of patients dying of disease, and approximately 30 per cent of the patients reported as alive having been followed for less than 1 year and therefore still at risk. The two major problems associated with this high death rate are the development of local or regional recurrence. Half of the patients developed either local or regional failure or a combination of the two, and this was associated with death in more than 60 per cent of cases. Again this is consistent with the situation which pertains with melanoma[31,32].

The results of treatment of patients with regional disease were dependent on the treatment regimen employed, and the poor overall results underline the importance of avoiding this problem if possible. Management with radiation alone was unsatisfactory as 80 per cent of patients died at a mean of 14 months after developing nodal disease. In contrast, when patients with regional disease were treated by lymph node dissection alone or in combination with radiation, 44 per cent were alive after a mean follow-up of 40 months These results parallel those following the treatment of many types of head and neck cancer, or in regional head and neck melanoma where results after the use of radiation alone to control regional disease are suboptimal[36,37]. We have previously reported that in patients with regional disease from squamous cell carcinoma of tongue[38] or lip[39], the results after radiation alone are poor. In addition, it is generally accepted that management of regional melanoma with lymph node dissection[35] results in approximately 30 per cent of patients surviving a further 5 years; in contrast, radiation of involved nodes although often providing symptomatic relief seldom results in 5-year survival[40].

Treatment of patients with Merkel cell tumour who have systemic disease is also difficult. Patients receiving no treatment survived for an average of 3–4 months after developing systemic disease, and those receiving radiation, chemotherapy, or radiation plus chemotherapy survived for less than 8 months. Again these results parallel those for melanoma where the overall response rate for chemotherapy is low and long-term survivors are few[41]; although radiation is effective in palliating symptoms resulting from systemic disease it has little effect in terms of prolongation of life[40].

Because local and regional failure were two major factors predisposing to death, and because the results of salvage treatment were poor, an optimal treatment regimen should include measures to minimize locoregional failure. In this respect guidance can be obtained from our understanding of melanoma, for which clearer treatment details have been established[42].

The 35 per cent incidence of local recurrence of Merkel cell tumour after excision alone was almost seven times higher than that noted in our review of almost 1000 melanoma patients (4·4 per cent[31]). Even if the patients with level 5 melanomas were considered as a subgroup, the incidence of local recurrence was still less than half that seen in the patients with Merkel cell tumour. On this basis it is reasonable to assess the results of the initial treatment of Merkel cell tumour in the light of what would be expected for level 5 melanomas or for melanomas >2–3 mm in thickness.

Few records of Merkel cell tumour supply detail of resection margins and this may explain the high incidence of local failure. For melanoma there appears to be little advantage in terms of minimizing local recurrence by taking a margin of >3 cm even for melanomas that are thick and known to have an unfavourable outlook[43,44]. In our previous review, the incidence of local recurrence for head and neck melanoma was 50 per cent higher than that for limb lesions[31,32], and this was largely on the basis of narrow margins being used in the head and neck for cosmetic reasons. For patients with Merkel cell tumour, nearly half of the lesions occur in the head and neck region, and the incidence of local recurrence for head and neck patients (44 per cent) was almost twice the value seen in patients with limb lesions (23 per cent). It is therefore likely that in many instances the resection margin in the head and neck patients may have been short of the desired 2·5–3·0 cm of clearance that would be optimal for a thick melanoma. Thus, rather than regarding the head and neck as an unfavourable anatomical site for Merkel cell tumours *per se*, the less favourable outlook may reflect inadequate local treatment.

The situation regarding prophylactic lymph node dissection in melanoma is debated. Although two prospective studies[45,46] have shown no advantage for patients with limb lesions, both have been criticized as having interpretive problems, and there are retrospective data from thousands of patients indicating a survival advantage in patients with lesions 2–4 mm of thickness[47]. Our review indicates that prophylactic treatment of regional nodes (either with surgery or with surgery coupled with radiation) is advantageous in patients with Merkel cell tumours. The incidence of loco-regional failure was almost halved in the patients who received nodal treatment in addition to excision alone.

Thus, when considering a treatment strategy for Merkel cell tumour, the following factors should be borne in mind:

1. This tumour behaves as if it were an aggressive variant of melanoma.
2. A local recurrence rate of 33 per cent indicates that an adequate margin of clearance (probably at least 2·5–3 cm), that is similar to that required for a thick melanoma, must be obtained.
3. Regional failure occurs in almost 50 per cent of patients with Merkel cell tumour after excision of the primary lesion alone, indicating a need to consider prophylactic treatment of regional nodes. Based on current knowledge of melanoma, prophylactic treatment should be considered in patients who have lesions likely to be associated with subsequent regional failure. This includes young patients, men, and patients with primary lesions in the head and neck.
4. Our review indicates that radiation alone is not optimal therapy for Merkel cell tumours, although some case reports describe complete resolution after radical radiotherapy[42]. However, adjuvant radiation following surgical resection appears to be effective in minimizing loco-regional recurrence.
5. As for melanoma, there is no effective chemotherapy for Merkel cell tumour, and management of systemic disease is probably best accomplished with palliative radiotherapy

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New trends in gallstone management

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Many new therapies for the management of gallstone disease have been pioneered in the past decade. The object of this review is to equip the surgeon with the answers to all of the questions a patient will ask about gallstone therapy; the review is therefore didactic as well as comprehensive.

Cholecystectomy has been performed for over 100 years and is the standard treatment for gallbladder stones with proven safety (mortality rate <1 per cent) and efficacy[1]. Nevertheless, even in the absence of complications and with a short hospital stay, up to two-thirds of patients spend more than 6 weeks off work[2]. There are patients who develop symptoms after cholecystectomy and 27–50 per cent of these complain of wound pain 1–2 years after operation[2,3]. In addition to the lengthy convalescence and long-term dissatisfaction following cholecystectomy, there is an increasing demand by patients for non-operative treatment of their gallstones. Many patients ask about their own suitability for such therapy because of their fear of an operation, the lengthy recovery period and their dislike of a 'large' unsightly scar.

The gallbladder is considered to be dispensible but its preservation may prevent the development of symptoms following cholecystectomy. Many gallbladders removed at operation function and appear remarkably normal with only microscopic changes of inflammation. There is evidence of a possible association between cholecystectomy and colonic carcinoma[4]. However, an intact gallbladder leads to gallstone recurrence and does not eliminate the risk of developing a gallbladder carcinoma.

In response to these arguments, over the past decade many new therapies for symptomatic gallstones have been pioneered and are now undergoing clinical evaluation. The purpose of this review is to examine the therapies available for the management of gallbladder stones including methods that are non-invasive, minimally invasive, and the newer surgical techniques.

Non-invasive treatment of gallstones

There are two completely non-invasive methods for the management of gallstones, oral dissolution therapy and extracorporeal shockwave lithotripsy.

Oral dissolution therapy

Dissolution agents. Several agents for gallstone dissolution which are administered either orally or by direct instillation into the gallbladder have been described and previously reviewed[5]. Dissolution therapy with bile acids was first used in 1970[6]. Two bile acids, chenodeoxycholic acid and its 7β-epimer, ursodeoxycholic acid, induce bile which is unsaturated in cholesterol, and these acids have been shown to be effective in dissolving cholesterol gallstones at doses of about 15 mg kg^{-1} day^{-1} and 8–13 mg kg^{-1} day^{-1} respectively[7]. Chenodeoxycholic acid has side-effects, particularly diarrhoea, which lead to poor patient compliance. Other side-effects are skin rash, changes in liver function tests, an increase in low density lipoprotein cholesterol and hepatotoxicity. Ursodeoxycholic acid is largely free from side-effects but is expensive. For these reasons, a combination of the two agents is commonly used and this is at least as a effective as either agent alone[8].

Selection. The ideal patient should have radiolucent stones measuring less than 15 mm in diameter (preferably <10 mm) to give the best surface area:volume ratio, and should have a functioning gallbladder. Using these selection criteria, less than 30 per cent of patients are suitable for oral dissolution therapy, but if account is taken of patient compliance, obesity and the presence of radiolucent insoluble pigment stones, this figure may be as low as 10 per cent. Improved selection can be obtained by computed tomography which is much more sensitive than conventional radiography in assessing calcification and can distinguish most pigment stones from cholesterol stones[9]. The effect of selecting patients by computed tomography on the results of bile acid therapy has yet to be determined.

Results. The overall efficacy of dissolution therapy is disappointingly low at about 38 per cent, and the treatment is prolonged (6–24 months)[10]. The finding on oral cholecystography of floating stones (consistent with a high cholesterol content) is associated with successful dissolution in 80–90 per cent of cases and is the best indication for this form of therapy[11,12]. When the stones are small in number (<1 cm in diameter within a well functioning gallbladder) and the patient complies with the treatment, the chance of success is about 60 per cent. Patients with larger stones which occupy most of the gallbladder volume are less likely to respond to bile acid therapy because of the greater stone burden and reduced surface area:volume ratio.

Complications occasionally develop during treatment but whether they occur with greater frequency than would happen spontaneously is unknown. Gleeson *et al.* have reported cystic duct obstruction in 20 per cent of patients after 4 years of treatment with ursodeoxycholic acid and other complications, such as recurrent biliary colic, pancreatitis and cholecystitis, in 16·8 per cent of patients after 18 months of treatment, necessitating referral for cholecystectomy[13]

Recurrence Recurrent stone formation is expected once treatment is stopped but to assume that all patients will develop stone recurrence is incorrect[14] In the British–Belgian Gallstone Study Group's trial, 83 of the original 93 patients with complete dissolution of their gallstones were followed up for 3·5–5 years[15]. At the end of 5 years, less than 50 per cent of the patients had developed stone recurrence and only two of 21 patients were symptomatic. The highest recurrence rate was noted in those patients with the most recent dissolution of their stones which indicates that stone clearance may have been incomplete. The rate was lower in patients who had remained stone-free for at least 9 months, and after 2·5 years there were no further recurrences to the end of the trial. O'Donnell and Heaton reported on 40 patients with complete dissolution of their gallstones of whom 27 had been followed up for over 4 years (range 0·5–11 years)[16]. The recurrence rate was approximately 10 per cent per year for the first 5 years and then

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reached a plateau without additional recurrences in the subsequent 6 years. In another study with a 12-year follow-up period, there were 96 complete dissolutions in 86 patients (some patients being treated for recurrent stones)[17]. The overall recurrence rate was 12·5 per cent in the first year rising to 61 per cent in the 11th year. In the early part of this study stone clearance was assessed by oral cholecystography rather than ultrasonography and so dissolution may have been overestimated leading to a higher recurrence rate. Only 10 per cent of patients who were treated for solitary stones developed a recurrence by the sixth year, suggesting that the majority of these patients are unlikely to reform stones in the future. Similarly in the British–Belgian Gallstone Study Group's trial only 15 per cent of patients treated for solitary stones developed recurrence after 4 years[18]. In both studies the rate of recurrence was significantly higher in patients treated for multiple stones. Such patients may have a greater degree of nucleating defects or more seeding factors increasing their propensity to reform gallstones.

The efficacy of postdissolution therapy is uncertain and while its long-term administration has been shown significantly to reduce the overall recurrence rate, this is mainly due to an effect on patients under 50 years of age[17]. In the British–Belgian Gallstone Study Group's trial, postdissolution therapy (3 mg ursodeoxycholic acid kg^{-1} day^{-1} was given to one-third of patients[15]. This group contained a larger number of patients with recent stone dissolution and these patients may have been at a greater risk of recurrence. However, the ursodeoxycholic acid-treated group showed a 50 per cent decrease in recurrence compared with projected rates. Continuing oral dissolution therapy indefinitely after stone clearance is usually inappropriate because approximately 40 per cent of patients will remain stone-free for at least 12 years. The immediate treatment of recurrent stones may not be indicated, especially if they are not symptomatic.

Summary. Providing patients are carefully selected, which may mean that as few as 10 per cent are suitable for treatment, oral dissolution therapy is moderately effective and will completely dissolve stones in 40–60 per cent of treated patients. The treatment takes up to 2 years for complete stone dissolution and is expensive. Stone recurrence will occur in approximately 50 per cent of patients within 5 years.

Extracorporeal shockwave lithotripsy

History and background. Extracorporeal shockwave lithotripsy was pioneered in Munich and was first used in 1980 for the treatment of kidney stones[19]. Later, it was applied to human gallstones implanted in the gallbladders of dogs[20] and in 1986 Sauerbruch *et al.* reported the successful fragmentation of gallstones in nine patients[21].

A shockwave is a highly distorted sinusoidal wave with a very rapid increase in amplitude and slower decline and it is created when the velocity of a pressure front exceeds the speed of sound[22]. In extracorporeal shockwave lithotripsy, the shockwaves are generated, focused and transmitted to the body through a liquid medium, usually water, which has a similar acoustic impedance to body tissues. The shockwaves spread through the body with little energy loss and therefore minimal tissue damage. Accurate positioning of the stone at the focal point of the wave is necessary for release of the high energy on impact which creates mechanical stresses and leads to fragmentation of the stone. Extracorporeal shockwave lithotripsy has the potential for causing significant soft tissue damage in the high pressure area around the focus of the shockwave[20,23,24]. Oedema of the gallbladder wall with vascular dilatation, petechial haemorrhages and variable mucosal denudation have been observed, but these changes, apart from mucosal denudation, were absent from gallbladders excised 24–48 h and 5 days after lithotripsy[25]. Therefore, the changes that occur seem to be rapidly reversible. Pulmonary damage reported in dogs has not been observed in patients[23].

Lithotripsy machines. All extracorporeal lithotripters incorporate underwater shockwave generation, a focusing system, a liquid medium to transmit shockwaves from the machine to the body and an imaging system to target the shockwaves accurately on the stone. The original first generation Dornier (Germering, Germany) machine used the spark-gap principle to generate shockwaves which were focused on the stone with a fluoroscopic guidance system. The treatment involved the patient being partially immersed in a water bath under general anaesthesia. Several second generation machines are on the market using three different systems to generate shockwaves: underwater spark discharge, piezoelectric elements and electromagnetic deflection of a metal membrane. Focusing of the shockwaves is achieved by an elliptical reflector, by arraying the piezoceramic elements on a hemispherical dish or by an acoustic lens. Most manufacturers have replaced the water bath with a compressible water bag and have both ultrasound and radiographic targeting systems.

Intravenous sedoanalgesia is still necessary when using the spark-gap system. The advantage of the piezoelectric system is that it causes minimal trauma and is almost painless; treatment can be performed on an outpatient basis without anaesthesia or analgesia[26] The disadvantage of the piezoelectric system is that a much higher proportion of patients require multiple treatment sessions to produce stone fragmentation. The more powerful shockwaves produced by the newer machines may overcome this difficulty.

Adjuvant therapy. Following stone fragmentation by lithotripsy the spontaneous discharge of stone fragments is unlikely to be complete. These fragments must negotiate the cystic duct with its valves of Heister, the common bile duct which has no peristalsis, and the sphincter of Oddi to reach the duodenum. Emptying of the normal gallbladder is a slow and incomplete process and in patients with gallstones is significantly impaired[27,28]. This impairment may be due to the physical presence of the stones, to chronic inflammation of the gallbladder wall or it may be related to the aetiology of stone formation. For these reasons adjuvant therapy is given, usually in the form of oral bile acids, but such treatment also impairs gallbladder emptying[27]. Although adjuvant therapy is thought to be necessary[29], studies to determine whether extracorporeal shockwave lithotripsy is effective without it are being conducted in the UK, the USA and Canada. Other adjuvant therapies that could be used are contact dissolution therapy or percutaneous cholecystolithotomy which can be applied to all types of stones.

Selection. Patients are usually selected for extracorporeal shockwave lithotripsy according to criteria laid down in the Munich study[30]. These criteria are based on the assumption that dissolution therapy is necessary to achieve complete clearance of the stone fragments, which means that only cholesterol stones are suitable for treatment. Stones should be radiolucent, less than 3 cm in diameter, and number not more than three. The gallbladder must function to allow bile acids to reach the stones and for the spontaneous passage of stone fragments. In the Munich study 28 per cent of patients referred with gallstones were accepted for treatment, but these patients may have been partially prescreened Examination of the number and size of gallstones in gallbladders removed at cholecystectomy suggests that only 15 per cent of patients are suitable for lithotripsy[31]. Darzi *et al* have questioned the validity of current selection criteria[32] and in their study of 124 patients, treated by lithotripsy combined with adjuvant bile acid and Rowachol® (Tillotts, Henlow, UK) therapy, only one-third of patients would have been selected using the Munich criteria. The remaining patients had stones that were more than 3 cm in diameter, more than three in number, or radio-opaque. Although the initial stone clearance was slower, overall clearance at 12–18 months approached 80 per cent (personal communication). This study indicates that many patients, previously regarded as unsuitable for extracorporeal shockwave lithotripsy, may be successfully treated.

Results. Sackmann *et al.* reported the Munich experience of the first 175 patients treated on the Dornier spark-gap machine with adjuvant bile acid therapy[30]. Sixty-five per cent of patients had solitary stones. Stone fragmentation occurred in all but one patient and 78 per cent of stones were reduced to fragments of less than 3 mm in diameter, with a retreatment rate of only 5 per cent. In another study, 38 patients were treated by piezoelectric lithotripsy and stone fragmentation was achieved in 34 patients (89 per cent) but 25 required multiple treatment sessions (range 1–5)[33]. Other centres have achieved fragmentation rates of 75–95 per cent with a variety of machines but with higher retreatment rates and larger fragment size than the Munich study[34–37]. Stone fragmentation has been most successful with solitary stones of less than 20 mm in diameter[30,35,37]. The poorer fragmentation rate with multiple stones and larger solitary stones may be due to the greater stone burden and the difficulties encountered in focusing shockwaves on a stone in the presence of multiple stones and fragments.

In the Munich study, complete stone clearance was achieved in 63 per cent of patients at 4–8 months, in 78 per cent of patients at 8–12 months, and in 91 per cent of patients at 12–18 months[30]. In patients with solitary stones of up to 20 mm in diameter the corresponding values were higher, respectively 78, 86 and 95 per cent Relatively poor clearance rates were observed for multiple stones, 29, 40 and 67 per cent respectively. The early results of the USA Cooperative Study in which 223 patients were treated by extracorporeal shockwave lithotripsy and adjuvant ursodeoxycholic acid therapy show that 90 per cent of patients with solitary stones of less than 20 mm in diameter and 36 per cent overall were stone-free 6 months after lithotripsy[37]. Approximately 1500 patients have been treated on the Wolf (Knittlingen, Germany) piezoelectric machine with a stone-free rate at 1 year of 73 per cent for solitary stones and of 51 per cent for multiple stones (European piezolith user meeting, unpublished results). Therefore, it seems that extracorporeal shockwave lithotripsy gives good results for solitary stones of up to 20 mm diameter but that its value for the treatment of multiple stones is less certain.

Complications following lithotripsy are common but are usually minor and include transient biliary pain (35 per cent), cystic duct obstruction (5 per cent), pancreatitis (2 per cent), skin petechiae (14 per cent) and transient haematuria (3 per cent)[30,38].

Recurrence. Only very limited data on gallstone recurrence following stone clearance by extracorporeal shockwave lithotripsy and adjuvant dissolution therapy are available because of the short follow-up period, but recurrence rates are expected to be similar to those following bile acid therapy. Sackmann *et al.* followed up 58 of the first 60 patients to become stone-free after lithotripsy for a mean period of 18 months (range 12–37 months) after discontinuation of adjuvant bile acid therapy[39]. The rate of gallstone recurrence was 9 per cent in the first year. The probability of stone recurrence was 11 per cent at 18 months but no further increase was observed up to 3 years. Darzi *et al.* have reported stone recurrence in five of 49 patients who have had complete stone clearance for a mean 8 months (range 1–20 months) after discontinuation of dissolution therapy[40]. In both studies the recurrent stones were small and multiple in all patients. Multiple tiny residual stone fragments undetected by ultrasonography may provide the nidus for recurrent stone formation.

Summary. Extracorporeal shockwave lithotripsy using second generation machines is usually painless and can be performed without anaesthesia on an outpatient basis. However, less than 15 per cent of patients with gallstones are suitable for treatment. The results of lithotripsy are promising with fragmentation rates of 75–90 per cent being achieved, followed by complete stone clearance in about 90 per cent of patients at 12–18 months. The best results are obtained with solitary stones which occur in 5 per cent of patients; the value of lithotripsy for treating multiple stones is less certain.

Minimally invasive gallbladder procedures

The ability to puncture the gallbladder percutaneously under radiological control or laparoscopic vision has resulted in the development of new diagnostic and therapeutic techniques for the management of biliary disease.

Percutaneous cholecystostomy

Over the past decade, experience has been gained with transhepatic puncture of the gallbladder[41,42]. This technique has been used for cholecystography and cholangiography, particularly when percutaneous transhepatic cholangiography has failed[43], for aspiration of bile or pus for culture in suspected cases of acute cholecystitis or empyema[43,44], and for biopsy of lesions within the gallbladder[45].

Direct percutaneous access to the gallbladder has opened new avenues for the non-operative management of gallstone disease and is being increasingly used, particularly in elderly and high risk patients, for the treatment of acute cholecystitis, empyema and the perforated gallbladder with localized abscess formation[43,46]. Drainage of the gallbladder under these conditions produces immediate relief of symptoms with resolution of pyrexia and white cell count. The procedure is performed with local anaesthesia and carries minimal morbidity and mortality. Although operation for the acute complications of gallstone disease is safe in the younger and fit patient, in the elderly mortality rates of 10–14 per cent are observed following urgent or emergency cholecystectomy[47,48] and of 5 per cent after surgical cholecystostomy[49]. After percutaneous cholecystostomy when the acute illness has resolved, the gallbladder and any bile duct stones can be removed by percutaneous or endoscopic techniques without the need for interval cholecystectomy.

Other therapeutic options made possible by percutaneous puncture of the gallbladder include contact dissolution of gallstones with solvents and mechanical stone removal via the percutaneous catheter tract.

Contact dissolution therapy

Background. Methyl tert-butyl ether (MTBE) and mono-octanoin are effective against cholesterol stones but MTBE is more potent and, at present, is preferred for the dissolution of gallbladder stones. MTBE is an alkyl ether similar to the anaesthetic agent, diethyl ether, but it is liquid at body temperature, boiling at 55°C. It is capable of dissolving more than twice its own volume of cholesterol. Stones have been dissolved *in vitro* in 60–100 min and when multiple human gallstones have been placed in dogs' gallbladders dissolution has occurred within 4–16 h[50]. As with bile acid therapy, MTBE is ineffective against pigment or calcified stones, but it can dissolve the cholesterol in mixed stones, leaving a residue of mud or gravel.

Technique. MTBE is administered via a 5 Fr percutaneous transhepatic catheter placed in the gallbladder under intravenous sedation and local anaesthesia[51,52]. Although endoscopic cannulation of the gallbladder is possible, most endoscopists cannot achieve the 74–100 per cent success rate in cystic duct cannulation that is claimed by some[53,54]. As the rate of dissolution is dependent on the flow of solvent over the stone surface, agitation and stirring within the gallbladder are important, and this has been achieved by continuously infusing and aspirating MTBE four to six times a minute by hand, for an average of 5·3 h per day, for 2–3 days[52]. A pump system has been devised to administer MTBE but is less reliable than by hand[55]. *In vitro* fragmentation of stones by a tunable dye laser before MTBE instillation has been shown to increase the speed of dissolution and may have clinical application[56].

Results. The Mayo Clinic has the largest published experience with MTBE dissolution of cholesterol gallbladder stones and the successful treatment of 72 out of 75 patients (96 per cent; residual fragments <5 mm in diameter) has been reported[52] Four patients (6 per cent) developed stone recurrence 6–16 months after treatment. Smaller studies report dissolution rates of 50 per cent[57] and over 80 per cent[58].

Despite the reported success, there are many problems with this technique, not least the side-effects which include severe burning pain, transient sedation due to systemic absorption (99 per cent is rapidly exhaled), intravascular haemolysis, nausea, vomiting, duodenal erosions, abnormalities in liver function tests, renal failure and destruction of certain catheter materials[52,57]. Early removal of the drainage catheter enables many patients to return to work within 1 week but a 2–5 per cent incidence of intraperitoneal bile leakage is reported[52].

The treatment is very labour intensive requiring considerable care and skill and, because of the potential for complications, is unlikely to become a standard method except in a few specialist centres.

Percutaneous cholecystolithotomy

History and background. Percutaneous cholecystolithotomy was originally described in 1985 in poor risk patients with acute cholecystitis treated by percutaneous cholecystostomy[59,60]. After dilatation of the transhepatic cholecystostomy tract, stones were removed in one to five sessions using baskets or forceps.

In 1988, Kellett *et al.* reported percutaneous cholecystolithotomy performed in a single stage using the transperitoneal approach[61]. The standard approach is transhepatic but large cannulae, which make stone extraction easier, cause unnecessary trauma to the liver. The transperitoneal approach is generally avoided because access is difficult with the risk of bowel puncture and intraperitoneal bile leakage. Hruby *et al.* assessed 100 computed tomography scans of the gallbladder in patients with gallstones to define the anatomical requirements for transperitoneal access and found that, because of the interposition of liver and colon, safe peritoneal puncture was not possible in 34 per cent of patients[62]. In a similar study, a plane of access that was free of colon could be found in all cases, but in only 13 per cent was the gallbladder fundus free of both colon and liver[63]. At the Middlesex Hospital, we favour the transperitoneal approach and have successfully performed fundal punctures of the gallbladder and dilatation of a track without complication in 94 out of 100 patients. Intraperitoneal bile leakage following transperitoneal puncture does not occur if the gallbladder is drained until a tract has formed.

Technique. The procedure has been adapted from the technique of percutaneous nephrolithotomy[64]. It is performed under general anaesthesia or local anaesthesia with intravenous sedation and takes 25–90 min.

Percutaneous cholecystography is performed and then the fundus of the gallbladder is punctured with a Kellett needle (152 mm long dwell sheathed needle, Becton Dickinson, Ontario, Canada), using a combination of ultrasonographic and fluoroscopic guidance. A guide-wire is placed in the gallbladder for the entire procedure as a safety measure. The track is dilated to 28–30 Fr using Teflon® (USCI) and telescoping metal dilators (Keymed, Southend-on-Sea, UK) before inserting an Amplatz Teflon sheath (Lewis Medical, London, UK). The gallbladder is inspected with a rigid cholecystoscope (Olympus, Keymed) and stones of up to 10 mm in diameter are flushed out or removed with forceps. Stones that are too large to pass through the Amplatz sheath can be fragmented by intracorporeal electrohydraulic, laser or ultrasound lithotripsy and removed piecemeal. The gallbladder is carefully inspected and a spot film is taken to ensure that all the stones and fragments have been removed. At the end of the procedure, a Foley catheter is introduced through the Amplatz sheath and placed on free drainage for 10 days. A 'tubogram' is performed and the catheter is removed provided that the biliary tree is clear of stones and there is no intraperitoneal extravasation of contrast. Hospital stay is short, patients typically being discharged 24–48 h after the procedure. Patients are able to return to full activity within 2 weeks and many return to work while the drainage catheter is *in situ*.

Selection. Suitability for percutaneous cholecystolithotomy is determined by ultrasound scanning of the gallbladder before and after a fatty meal. This assesses the number and size of stones, the position and function of the gallbladder, and the thickness of its wall. Over 75 per cent of all patients with symptomatic gallstones are accepted for percutaneous cholecystolithotomy. Stone type, size and number do not affect selection. The only patients who are unsuitable for the procedure are those with contracted, thick-walled gallbladders, not only because the gallbladder is diseased but also for technical reasons. The gallbladder that is non-functioning because of a stone impacted in Hartmann's pouch does not constitute a contraindication and patients with acute complications of gallbladder stones, particularly the elderly and unfit, are also suitable. Although most percutaneous cholecystolithotomies are performed in a single stage, the obstructed or acute gallbladder is electively decompressed by percutaneous cholecystostomy for 7–10 days to allow the acute phase to resolve or the stone to disimpact before cholecystolithotomy.

Results. In our experience, percutaneous cholecystolithotomy has been successful in 89 out of 100 patients. Eighteen per cent of these patients presented with acute complications of gallstones and 30 per cent were regarded as high risk or unfit for cholecystectomy. Failures were due either to failed gallbladder puncture and dilatation, or to residual cystic duct stones. Failed puncture has usually been due to a 'floppy' gallbladder which invaginates and slides away from the advancing needle and dilators. A cholecystostomy catheter with a removable anchor to secure the fundus to the abdominal wall is being developed to overcome this problem[65]. Only one of the five patients with residual cystic duct stones had a functioning gallbladder before treatment and only two of these patients have undergone cholecystectomy for persistent symptoms. In their separate experience, Chiverton *et al.* report successful stone clearance in 56 out of 60 fit patients (93 per cent) with non-acute gallstone disease[66]. None of their patients had cystic duct stones. In the Middlesex Hospital series there has been no death associated with percutaneous cholecystolithotomy and only 13 of our patients have developed complications, which include transient cholangitis and subhepatic bile collections. Two of the latter underwent percutaneous or operative drainage. Other reported complications are colonic puncture and pancreatitis and these have been managed conservatively[66]. Most complications occurred with the early cholecystolithotomies when we were at the bottom of the learning curve. It is too early yet to establish whether recurrent stone formation will be less than that following other non-operative treatments. Percutaneous cholecystolithotomy will not affect the recurrence of stones due to *de novo* formation.

Laparoscopic cholecystolithotomy

In this procedure, the gallbladder is accessed under direct vision using a laparoscope. Perissat *et al.* then introduce a rigid cholecystoscope through a trocar sheath positioned in the right hypochondrium and, following pulverization of the stones with an ultrasonic lithotripter, remove them by continuous irrigation and aspiration[67]. The gallbladder is drained for 7 days. Seventeen patients with biliary colic have been treated by this method with minimal morbidity. Experimental work in pigs has shown that the gallbladder incision can be successfully closed using staples and fibrin glue, avoiding the need for drainage after the procedure[68]. The need to provide biliary drainage is certainly a disadvantage of both the laparoscopic and percutaneous techniques.

Minicholecystostomy with radiological stone removal

Ultrasound-guided surgical cholecystostomy, under sedation and local anaesthesia, has been described in 36 elderly, high risk patients with acute cholecystitis or severe biliary colic[69]. On the seventh to tenth day after operation, stone extraction was attempted using radiological techniques via the 24 Fr cholecystostomy tract. Ninety-seven per cent (35 out of 36) of gallbladder, 86 per cent (six out of seven) of cystic duct, and 63 per cent (five out of eight) of bile duct stones were successfully extracted through the short surgical tract. Minicholecystostomy does not appear to have any advantages over the newer, less invasive technique of percutaneous cholecystolithotomy which can also be performed under local anaesthesia in the high risk patient.

Summary

Minimally invasive techniques are suitable for over 70 per cent of patients with gallstones and although the majority of patients treated have functioning gallbladers, a patent cystic duct is not essential. Compared with the non-invasive treatments for gallstones, these methods are successful in over 85 per cent of patients, produce minimal scarring (a single 1 cm scar for percutaneous cholecystolithotomy) and the treatment is complete with full recovery within 2–3 weeks.

New techniques for cholecystectomy

Patients are increasingly demanding non-operative treatment for their gallstones mainly due to their fear of an operation with its legacy of a 'large' scar and the long duration of recovery. These criticisms of conventional, cholecystectomy can be overcome by modifying surgical technique.

Laparoscopic cholecystectomy

At present, there is much interest in laparoscopic cholecystectomy. Although well over 2500 of these operations have been performed worldwide, only two centres have reported their results[67,70].

Technique. The procedure is performed under general anaesthesia and with experience can be performed in 40–90 min. Following standard laparoscopy through a 10 mm umbilical incision, two 5 mm trocar sheaths are introduced in the right hypochondrium, for forceps to grasp the gallbladder and for an aquapurator for irrigation and suction which can also act as a liver retractor[70]. A second 10 mm trocar sheath is placed either in the left hypochondrium or to the right of the midline through which the dissection is performed using a hook-shaped diathermy probe, forceps and scissors, a clip applicator for the cystic artery and duct, and forceps to extract the gallbladder. The latter incision may need to be enlarged to deliver the gallbladder with its stones through the abdominal wall. Peroperative cholangiography can be performed by cannulating the cystic duct in the normal way. Bile duct stones may be extracted by formal exploration or by endoscopic retrograde cholangiopancreatography and sphincterotomy. Perissat *et al.* use a similar method but extract the gallstones after ultrasonic pulverization through a cholecystotomy before proceeding with cholecystectomy[67]. Dissection with laser energy involving expensive equipment is an alternative to the use of diathermy but this does not appear to have any advantage over the diathermy hook for meticulous haemostasis and ease of dissection.

Results Dubois *et al.* have performed over 400 laparoscopic cholecystectomies using this technique with minimal morbidity and no mortality (personal communication). In their preliminary report, 36 out of 39 patients underwent successful laparoscopic cholecystectomy but two patients required laparotomy for uncontrolled cystic artery bleeding and for drainage of a subhepatic bile collection[70].

Laparoscopic cholecystectomy is an attractive alternative to standard cholecystectomy but, as with laparoscopic appendicectomy, is suitable for the more straightforward, easy operation. With greater experience and instrumentation the operation can be performed in the presence of adhesions and acute inflammation, and stones can be removed from the bile duct using techniques developed by endoscopists. The main advantages of this technique are the cosmetic aspects, minimal wound pain with complete resolution within a few days, the short hospital stay (mean 2 days), and the ability of many patients to return to work within a week of operation[70]. However, as with all new techniques, there is a learning curve and initially the procedure may take 3–4 h to perform. It will be attractive to many surgeons as a technical exercise but it is questionable whether it has a major advantage over the modern minicholecystectomy with a single 5 cm incision.

Minicholecystectomy

Technique. Cholecystectomy may be safely performed through a small transverse incision (4–6 cm)[71–73] One method uses a stabilized ring retractor (Bookwalter retractor, Codman) which comes with a variety of fixed and malleable blades and provides accurate, fixed retraction with excellent exposure despite the small incision[73]. The surgeon's hand does not enter the abdomen at any stage and the operation can be performed without an assistant. The gallbladder is dissected retrogradely, using Turner–Warwick's diathermy scissors to ensure haemostasis throughout. Peroperative cholangiography is performed, securing the cholangiocatheter with a haemoclip. The cystic duct and artery are also clipped and the wound is closed without drainage. No modification of the incision is required for the more difficult gallbladder, for exploration of the bile duct or for choledochoduodenostomy. The cosmetic result is excellent, especially when the incision is made in a skin crease and closed with an absorbable subcuticular skin suture.

Results. In our own experience, over 80 per cent of the patients are discharged on the third day after operation, although a mean hospital stay of only 1·5 days has been reported[71]. Patients require less analgesia after the operation than after standard cholecystectomy and they are able to return to work after an average of 18·6 days. With further modification of the retractor and improved illumination it should be possible to perform cholecystectomy through an even smaller incision.

Discussion

Several new therapies for the management of gallbladder stones are undergoing evaluation. The immediate results of these treatments are very promising with a high percentage of selected patients being cleared of their gallstones but, as yet, their long-term success is unknown. Oral dissolution therapy and extracorporeal shockwave lithotripsy, using current selection criteria, have limited application being suitable only for the 10–30 per cent of patients with pure cholesterol stones. The prolonged drug treatment is costly and inconvenient to the patient, and with extracorporeal shockwave lithotripsy there is the added initial expense of the lithotripsy machine Other non-operative treatments are more invasive and require hospital admission. MTBE therapy is limited to the treatment of cholesterol gallstones but percutaneous cholecystolithotomy can be offered to over 75 per cent of patients with any type, size or number of stones, and the treatment is complete with full recovery within 2–3 weeks.

The main disadvantage with all therapies that preserve the gallbladder is stone recurrence. Some recurrent stones will be due to residual stones or fragments and others to *de novo* formation. Radiological assessment of stone clearance may not detect very small fragments that can act as a nidus for new stone formation. Following treatment with MTBE, many patients are left with an insoluble residue within the gallbladder but even after endoscopic clearance, as in percutaneous cholecystolithotomy which should be more thorough, it is often difficult to remove tiny fragments and dust which are adherent to or embedded in the mucosa. Biliary sludge is not an uncommon finding on ultrasound scans but is of uncertain significance. Recent evidence indicates that it may be a direct gallstone precursor and, if so, its presence could be used to identify those patients at risk of reforming stones[74]. There seems to be a population of patients who are unlikely to develop recurrent stones and it may be that these patients no longer produce lithogenic bile. In the future it may be feasible to combine cholecystolithotomy with permanent ablation of the gallbladder by thermal or chemical injury to remove the risk of gallstone recurrence[75,76]. Substances that alter cholesterol metabolism such as hydroxymethylglutaryl coenzyme A reductase blockers and non-steroidal anti-inflammatory agents may have a role in gallstone prevention[77].

How should patients with recurrent stones be managed? Current evidence suggests that the majority of patients with asymptomatic gallstones can be managed expectantly[78]. Therefore, only patients with symptomatic recurrent stones need to be actively treated and they can be managed again by non-operative means. The risk of recurrence should be considered when choosing between operative and non-operative therapy, particularly in young, fit patients with no increased operative risk. The advantages of non-operative treatment for high risk patients such as the elderly, obese and medically unfit are not disputed. The newer operative techniques of laparoscopic cholecystectomy and minicholecystectomy require greater technical skills but have the advantages of less morbidity, shorter convalescence and greater acceptability to the patient than standard cholecystectomy.

Critical evaluation of all new methods of managing gallstones is needed with particular reference to symptom relief, selection of patients, long-term outcome and cost-effectiveness. The results of trials of extracorporeal shockwave lithotripsy are awaited[79] but randomized controlled trials comparing non-operative methods with the newer surgical techniques of laparoscopic cholecystectomy and minicholecystectomy, as well as the standard operation, need to be performed. Although cholecystectomy is the most effective long-term treatment for gallbladder stones, it is being challenged by many new non-operative therapies. We believe that it is time to modify surgical technique to maintain cholecystectomy as the standard treatment for gallstones in the 1990s. Whether laparoscopic cholecystectomy, minicholecystectomy, or even a minimally invasive method proves to be the preferable treatment, there will be an increasing requirement for the specialist, with experience of all the above techniques, to offer an individualized approach to the varied presentation of biliary tract stones.

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Conventional *versus* laparoscopic cholecystectomy and the randomized controlled trial

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We considered using a randomized trial to assess the value of laparoscopic cholecystectomy in the treatment of symptomatic gallstones. The pros and cons for the timing of such a trial were in favour of not beginning the trial until surgeons learned to use the new procedure safely and effectively, and until key endpoints and outcome indices could be identified and assessed using valid measures. Instead an observational study was implemented to monitor the learning curve of surgeons as they mastered the laparoscopic equipment and procedures, and to assess the responses of the patients to the procedure. In the first 100 patients, the procedure proved to be as safe and feasible to use as conventional surgery, and there were strong benefits in terms of quicker recovery of the patients with less pain, discomfort, and a reduced length of hospital stay. The responses of the surgeons and the patients to the new procedure now place ethical constraints on the planning of a randomized controlled trial. Currently, comprehensive surveillance and monitoring of laparoscopic cholecystectomy is the only realistic method with which to assess the impact of this new technology in our clinic.

Cholelithiasis is one of the most common diseases in Western European countries, with a prevalence between 5 and 22 per cent[1–9], and cholecystectomy has been the accepted method of treating patients with symptomatic gallstones. The purpose of cholecystectomy is the relief of symptoms and disability and the prevention of mortality Although the mortality rate of the operation (overall less than 0·1 per cent but up to 10 per cent if elderly patients are operated on for complications caused by gallstones[9,10,11]) and the rate of complications following cholecystectomy are low, most patients still experience difficulty because of postoperative ileus, pain, discomfort, disability and long convalescence. This has led to the development of a number of alternatives, including dissolution of gallstones with cholelitholytic drugs[11], extracorporal shock-wave lithotripsy with or without adjuvant bile acid dissolution[12,13] and various techniques of laparoscopic cholecystectomy[10,14,15,16]. Laparoscopic cholecystectomy is the most promising new technique for the treatment of cholelithiasis in terms of reduction in postoperative morbidity and length of convalescence.

However, as correctly pointed out in two recent editorials[17,18] – one entitled 'The laparoscopic evolution – walk carefully before we run' – the authors asked for a controlled evaluation of the new technique. They suggested prospective randomized controlled trials to define the indications for the laparoscopic approach and to confirm its benefits when compared with the standard operation of open cholecystectomy. When we started doing laparoscopic cholecystectomies in Cologne in October 1989, we intended to set up a prospective randomized trial after confirmation of the feasibility and safety of the new procedure in our hands. The protocol had to meet all accepted criteria for assessment including safety, applicability, benefit for the patient and the surgeon, efficacy and cost–benefit effectiveness, because it is no longer acceptable or tolerable to describe the clinical significance of technologies in terms of case studies or empirical judgements[19]. In setting up the protocol, however, we were confronted with several basic problems which had to be solved before starting a trial. The purpose of this paper is to point out some of these problems and to present our solutions for debate.

When is it appropriate to carry out a randomized controlled trial?

After the introduction of laparoscopic cholecystectomy in our clinic in October 1989, the timing of a possible randomized controlled trial for its comparison with the well established conventional cholecystectomy was discussed repeatedly. Examining the literature to learn through the example provided by other innovations in surgery (i.e. shunt surgery for portal hypertension[20,21], coronary artery bypass grafting[22,23,24], jejunocolic and jejunoileal bypass surgery[25], or total hip replacement[26]) it became obvious that the timing of randomized trials was and still is a highly controversial issue. Some people insist that clinical trials must be done as early as possible in the evaluation of new therapies[27] whereas others have argued against them, especially in surgery[28]. There is, however, unanimous agreement that a new treatment should be introduced in a manner that allows prompt and reliable evaluation of its efficacy and safety. The question is: how to do this promptly and reliably?

Pro: initiate a randomized controlled trial as early as possible

Chalmers[27] has made an especially strong case for randomizing the first patient to receive a new drug, procedure or operation and has provided a number of compelling arguments against 'pilot trials'. The concept stems from recognition of the influence of pilot trials in postponing or eliminating a definitive therapeutic trial. If one considers for example the disorderly history of shunting procedures for portal hypertension, decades were wasted by the failure to introduce, standardize, and carry out randomized controlled trials from the beginning[29]. Increasing and unrestricted use of a new operation such as laparoscopic cholecystectomy increases the uncertainty about its value. In the absence of an explicit and detailed experimental protocol, institutions and surgeons are apt to vary considerably their selection of patients and choice of operative technique as well as their criteria for subsequent evaluation Purists even state that it is scientifically and ethically inexcusable not to undertake randomized controlled trials as soon as possible.

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Con: do not initiate a randomized controlled trial as early as possible

There are strong arguments for not randomizing the first patient in the evolutionary phase of a new operation, especially if the new operation requires training as is the case for laparoscopic cholecystectomy. Few general surgeons have any experience in using a video monitor to watch instruments inserted through holes in the abdomen. In contrast to medical trials, which are almost independent of any special skill, the results of surgical trials vary according to the skill and experience of the surgeon. Sometimes proper information on the feasibility of a trial is lacking[30]. Before conducting a trial, the investigator needs to have the necessary knowledge and tools. He or she must have information about the safety of the intervention and the endpoints to assess, and must have validated techniques to conduct the assessment.

Another aspect of timing is the consideration of the relative stability of the intervention. An early randomized trial can be rendered obsolete by advances in surgical technique. As laparoscopic cholecystectomy is a completely new approach in gallbladder disease, improvements in the operative technique and surgical skills, as well as a constant development of surgical instruments, can be expected within a short time. A good example to support this argument, and one which was widely discussed in literature, was the randomized study of coronary artery bypass surgery, the Veterans Administration trial[24]. This trial did not have the expected impact on coronary surgery because it was criticized for poor early operative results and lack of relevance to current experience, not for fundamental flaws in the design[31].

Surgical journals contain a number of examples of innovations which would not have stood a chance of adoption if they had been immediately subjected to a randomized trial. Langenbuch published the first account of cholecystectomy in 1882[32], having taken the utmost care, including care in the selection of the first patient To quote Van der Linden[28]: 'In spite of this and in spite of the fact that the operation was successful, he engendered much criticism among his peers[33]. Fortunately, Langenbuch did not randomize his first patient, neither did he run a trial. Such a trial, performed by surgeons unfamiliar with a procedure which requires careful training and thorough knowledge of biliary tract anatomy would have given a very unfair picture of an operation, the value of which cannot be doubted'.

After weighing the pros and cons for the timing of a randomized controlled trial of 'conventional *versus* laparoscopic cholecystectomy' we were in favour of not starting such a trial from the very beginning. Instead, consensus was obtained first to initiate a careful observational study of the new procedure in parallel with a study of conventional cholecystectomy using the same detailed and standardized protocol. This observational study was intended to be replaced by a randomized controlled trial after demonstration of safety and feasibility. The purpose of the observational study was to audit outcome by prognostic factors such as age, sex, diagnostic categories and severity of the condition and to identify the therapeutic uncertainty justifying a randomized controlled trial. Furthermore all factors contributing to the 'learning curve' had to reach an acceptable degree of variation or plateau which was unlikely to change greatly. We published our description of the outcome of laparoscopic cholecystectomy in 100 patients comprising this observational study[16] and a summary is given in *Table 1*. The Cholecystectomy Study Group is now meeting again to discuss the results and the prerequisites to be fulfilled before switching over to a more advanced assessment, ideally a randomized controlled trial, to allow reliable evaluation of the benefits and limitations of the new laparoscopic technique.

Table 1 *Laparoscopic cholecystectomy demographic data, characteristics and major endpoints estimated in the observational study on the first 100 patients operated on from October 1989 to May1990 (from Spangenberger* et al.[16])

Demographic data	
Total number of patients (*n*)	100
Sex (*n*)	
Male	18
Female	82
Age (years)	45 (25–78)*
Weight (kg)	64 (41–130)*
History of biliary tract symptoms (years)	
Cholelithiasis	2 (0–27)*
Pain	1 (0–20)*
Colic	0·5 (0–27)*
Severity of biliary tract symptoms (classification scale according to McSherry *et al.*[38]	
Grade 0 (*n*)	12
Grade + (*n*)	65
Grade ++ (*n*)	23
Severity of condition (ASA classification)	
ASA I (*n*)	29
ASA II (*n*)	55
ASA III (*n*)	16

Major endpoints estimated	
Mortality (number of patients)	0
Complications during operation	
Iatrogenic leak from bile duct	1
Complications after operation	
'Major'	
Ileus (*n*)	1
Peritonitis (*n*)	1
'Minor'	
Thrombophlebitis (*n*)	1
Wound discharge (*n*)	10
Haematoma (*n*)	1
Time of operation (min)	
Patient 1–50	120 (60–240)*
Patient 51–100	90 (30–210)*
Time of hospitalization (days)	
Preoperative	2 (1–9)*
Postoperative	3 (1–15)*
Pain intensity (VAS scale)	
1st postoperative day	33
2nd postoperative day	23
3rd postoperative day	10
Discharge	7
Nausea (*n*)	
Day of operation	51
1st postoperative day	24
2nd postoperative day	8
3rd postoperative day	1
Vomiting (*n*)	
Day of operation	22
1st postoperative day	6
2nd and 3rd postoperative days	0

* Median (range); ASA, American Society of Anaesthesiologists

Can a randomized controlled trial really be performed?

In focusing attention on procedures with which to evaluate the efficacy of a feasible new operation or to compare its efficacy with that of competing operations there is a choice of approach ranging from case series with or without historical controls to a randomized controlled trial. Among investigators there is unanimous agreement that a properly planned and executed randomized controlled trial is the best available method for evaluating alternative treatments including surgical operations.

Surgeons have had considerable difficulties in learning to put aside judgements based on experience or tradition and it was Goligher who set up the first randomized controlled trial in surgery (comparing vagotomy with gastroenterostomy or antrectomy with subtotal gastrectomy in the elective treatment of duodenal ulcer)[34]. This report spurred surgeons all over the world to conduct randomized controlled trials but it is still true that most clinical research in surgery relies on comparisons with historical or contemporary non-random controls[35]. New operations may be more difficult to evaluate than new drugs[36]. Furthermore, recent developments in the application of ethical principles coupled with problems of selective enrolment of patients have clearly restricted the use of randomized controlled trials as clinical research tools[35,37]. This also applies to our intended randomized controlled comparison of conventional as opposed to laparoscopic cholecystectomy. The two basic problems, namely 'the selection bias problem' and 'the ethical problem' will now be discussed.

The selection bias problem

One of the prerequisites of a trial is that a sufficient number of patients can be recruited within a reasonable period of time so that there is a high likelihood of detecting a significant difference in event rate between the groups. The study population as a subset of the general population requires specification of criteria for eligibility. These criteria must relate to safety and study design. To fulfill these prerequisites only those patients should be enrolled who are considered suitable for both operations. Our eligibility criteria in the present context were to be: age >18 years, elective operation on patients with a history of symptomatic cholelithiasis (severity of symptoms scale 0 to ++ according to McSherry[38]), ultrasonographic confirmation of gallstones, no signs of infection or cholestasis clinically or by assessment of laboratory data, and patients classified as ASA I–III according to the American Society of Anaesthesiologists.

In a retrospective audit of patients operated on in our clinic in the year before starting laparoscopic cholecystectomy, we found that only 70 patients fulfilled these criteria This number was considered far too small to start a randomized controlled trial. However, the very high public interest in laparoscopic cholecystectomy and the publicity surrounding our clinic following reports of the first successful operations in Germany led to a rapid increase in the number of eligible patients with gallbladder symptoms in our clinic. The patients were no longer recruited only from the area around Cologne but came from elsewhere in Germany and Europe. The potential advantage of this increased recruitment of patients, namely that it would enable us to run a trial, was diminished by the fact that all these patients wanted only the new 'minor' invasive technique that they had heard about. The change in recruitment pattern led to our collecting a highly selected group of patients not comparable with the historical 'control' cholelithiasis patients in our clinic. Of the 100 patients who had laparoscopic cholecystectomy[16] 77 were classified as grade 0 to + (McSherry[38]), a grading which applied to only about 10 per cent of the patients who were operated on for gallstones previously. Furthermore, after the introduction of the laparoscopic technique in October 1989 no patient was denied the new operation on the basis of the eligibility criteria outlined above. The reason was not only to get more experience with the new technique but (and much more importantly) that the parallel analysis of the endpoints of postoperative pain, nausea, convalescence and in-hospital stay were strongly in favour of the new technique.

Our 'historical experience' was not, however, based on a well documented database using the new endpoints. To run a trial under these circumstances brought us to the next problem, the ethical problem.

The ethical problem

People have debated the ethics of clinical trials for as long as they have been undertaken. The fundamental ethical justification for a randomized controlled trial is that neither the patient nor the surgeon will have a preference for one arm over another; ignorance of the respective merits of the two techniques is essential. It is quite wrong for surgeons to engage in a randomized controlled trial unless they are convinced that the answers to the questions being addressed are truly unknown No trial is justified unless it is scientifically sound and the need for any study should be subject to evaluation using available information[39]. When a new technique is introduced there is only scanty information available. It was therefore one of the aims of our observational study to identify the field of therapeutic uncertainty justifying a randomized controlled trial. The first two of the three basic ethical principles (respect for persons, beneficence and justice) consonant with the major traditions of Western countries as identified in the Belmont Report[40] have to be considered.

According to the principle of autonomy, patients have the right to make their own decision about treatment. Application of this principle to clinical research translates into informed consent[41]. Informed consent requires full disclosure of the available information regarding the potential benefit and harm of any procedure. Despite the fact that patients were informed that only preliminary information was available for the new laparoscopic technique and that there was a great deal of medical uncertainty, it proved impossible to translate this to the patients at a time of enthusiasm for the new technique. Patients were strongly in favour of it because of the smaller scar, diminished postoperative pain, shorter hospital stay and the more rapid physical recovery. Accepting the ethical principle of autonomy means that randomized controlled trials have become obsolete for alternative treatments that are of concern to the patients The intended randomized controlled trial then joins other obsolete controlled trials such as comparisons of partial mastectomy and total mastectomy or colonic anastomosis with or without colostomy, as outlined recently by Oettinger and Beger[37].

The second principle (beneficence) is directly relevant to the ethics of evidence. It is unethical to use a powerful therapeutic procedure without sound assessment of risks and benefits. To meet this principle the safety of the laparoscopic technique was carefully evaluated. All the patients in the observational study (*Table 1*) were discussed separately in open conference with members of the Cholecystectomy Study Group, other surgeons from the clinic and invited guests There was unanimous agreement that the new technique, in the selected group of patients operated on, was as safe as the conventional technique in the hands of surgeons with specific experience.

In our clinic only three surgeons were involved in all of the 100 operations. There were no deaths and the only three major complications occurred early in the series and were considered avoidable. An iatrogenic injury to the common bile duct resulted in one patient undergoing a mini-laparotomy with conventional cholecystectomy and T tube drainage. Two further complications occurred postoperatively which made laparotomy necessary; one 44-year-old woman with an initially uneventful postoperative course returned 4 weeks later with a subacute small bowel obstruction. Laparotomy revealed that the small bowel serosa had been sutured to the abdominal wall. One other patient developed an acute abdomen on the first postoperative day. Laparotomy revealed early peritonitis with positive bacteriological culture (*Escherichia coli*). After treatment all three patients were discharged from hospital and there have been no further complications to date.

The benefits of laparoscopic cholecystectomy as compared with conventional cholecystectomy were evaluated from published data, historical data from our clinic and the personal experience of the senior surgeons. This revealed a strong benefit for the new technique with regard to all endpoints concerned with patients' discomfort and disability (postoperative pain intensity, nausea, vomiting, convalescence) as well as duration of hospital stay. There was a consensus that a randomized controlled trial was not justified at this time in patients similar to those enrolled in the observational study. The group was aware that this decision was based on insufficient information about the results of the conventional technique. Nevertheless, the fundamental ethical justification for a randomized trial – that the participating surgeons should have no preference for one arm over another – was not fulfilled.

Where do we go from here?

Ethical restraints and resistance by patients and surgeons to allowing the choice of operation for symptomatic gallstones to be decided by chance mean that we have to consider alternatives to randomized clinical trials. A system of comprehensive surveillance seems to be the only realistic alternative at a time when the laparoscopic procedure is spreading like 'wildfire'[41]. Continuing surveillance should be maintained at a level which will allow long term evaluation of both the new and the old techniques. Such surveillance should be carried out at the minimum level necessary. For this purpose, an extensive (as many institutions as possible) computer based databank is versatile and appropriate. We therefore strongly support the most recent initiative of the Society of American Gastrointestinal Endoscopic Surgeons who set up the International Retrospective and Prospective Multi-Institutional Laparoscopic Cholecystectomy Study (study co-ordinators: G. Berci and J. Sackier), It is the responsibility of all participants to report complete, accurate, and honest audit of outcomes in order to make this assessment tool reliable. This database will then reveal the value of the new laparoscopic technique in comparison with alternative treatments and will answer questions of therapeutic uncertainty which may justify randomized controlled trials in the future.

To justify a randomized controlled trial in conditions where uncertainty is recognized requires extensive discussion of all prerequisites outlined above. The discussion in our Cholecystectomy Study Group revealed that it will never be easy to run such a trial in this field. On the basis of current knowledge and experience our group reached a consensus that the efficacy of the laparoscopic technique is most questionable for patients with acute cholecystitis evidenced by tenderness in the right abdomen, fever and leucocytosis (+ + + according to McSherry[38]). Despite the fact that the study protocol for a randomized controlled trial in this group of patients had been approved by an independent ethics committee at our university we are at present unable to perform the trial. The reason is that our operation facilities are totally blocked by patients with symptomatic cholelithiasis awaiting elective laparoscopic operation. We are therefore unable to enrol a sufficient number of eligible patients in our clinic alone. A multicentre trial is currently not possible because of lack of experience with the laparoscopic techique in otherwise suitable surgical clinics.

Two further problems are connected with the fact that the two treatment arms (laparoscopic *versus* conventional cholecystectomy) can be distinguished by the patients involved. As the trial proceeds it is unavoidable that impressions about results will be conveyed to new patients entering the trial. These impressions will interfere decisively with further randomization and the assessment of results as judged by the patient. The bias in the assessment of the results is considerable as most of the relevant endpoints, such as pain relief and fatigue, will rely only on patients' evaluation.

Conclusions

Laparoscopic cholecystectomy is a considerable advance in the treatment of gallbladder disease. Many consider that all hopes for a critical assessment of the procedure have to all intents and purposes disappeared. We do not share this opinion but hope that the time will come again to perform randomized controlled trials in specific subsets of patients with gallstone disease. Moreover, future trials comparing laparoscopic cholecystectomy with alternative medical therapies, in particular extracorporeal shock-wave lithotripsy, or trials comparing lithotripsy plus postponed laparoscopic cholecystectomy with early laparoscopic cholecystectomy in high risk patients with gallstone disease will further reveal its value. The safe application of the laparoscopic technique will also renew old controversies regarding the treatment of asymptomatic gallstones in the near future.

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Laparoscopic cholecystectomy: the Dundee technique

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A total of 61 patients was subjected to laparoscopic cholecystectomy. The procedure was completed in 60 cases and converted to open operation in one (2 per cent). The morbidity rate was low (total 7 per cent, major 2 per cent, blood transfusion rate 5 per cent). The median duration of the laparoscopic cholecystectomy with cholangiography was 135 min (range 65–270 min). The operation took less time to complete in patients with functioning gallbladders than in those with non-functioning fibrotic organs (median 120 versus *175 min). The majority of patients required opiate analgesia despite infiltration of the stab wounds with bupivacaine. The mean(s.d.) hospital stay was 2·9(1·5) days. The median time to resume work or full activity after discharge was 11 days.*

Since the operation was first performed in man by Phillipe Mouret in Lyon in 1987 (personal communication), laparoscopic cholecystectomy has become firmly established in a number of centres in Europe and North America[1–5]. Unlike all the newer non-surgical treatments for gallstone disease introduced into clinical practice during the past 15 years, it is applicable to the majority of patients with gallstone disease and provides definitive therapy, abolishing the problem of recurrence. The essential attribute of the laparoscopic approach, which is as invasive as the equivalent open operation, is the reduction of the 'trauma of access' without compromise of the exposure of the operative field. This appears to diminish the catabolic response and is associated with accelerated recovery and virtual abolition of wound-related complications.

The Dundee technique based on a 2-year period of animal experimentation differs in some respects from that practised in Europe and North America. This paper outlines these technical points and reviews our initial experience.

Essential features of the Dundee technique

Patient position, catheterization and nasogastric suction

All but the first four patients were operated upon under general anaesthesia in the supine position with the surgeon on the left side and the assistant on the right, using two TV monitors. This provides better access than the lithotomy position and is less likely to cause compression trauma to the calf veins particularly during long operations.

We consider that catheterization of the urinary bladder is essential before all laparoscopic procedures. Nasogastric suction via a Ryle's tube is essential to keep the stomach and duodenum deflated throughout the procedure. Both the urine catheter and the Ryle's tube are removed at the end of the operation.

Pneumoperitoneum, position and size of trocar/cannulae

The procedure starts with insufflation of the peritoneal cavity using a Veress needle and an electronic variable flow pressure-controlled insufflator. The Veress needle has a spring-loaded stylet which automatically converts the sharp point of the needle to a rounded one once the peritoneum is breached. In previously unoperated abdomens, the Veress needle is inserted via a stab wound below the umbilicus. Once the position of the needle is confirmed by the saline syringe injection/aspiration test, it is connected to the insufflator which is preset to insufflate to an intra-abdominal pressure of 12–15 mmHg. It is important that the insufflation is carried out using a low flow setting (1·0–1·5 litres/min) as otherwise cardiac arrhythmias may be encountered. Higher flows can be used with safety once the desired pneumoperitoneum has been established. At this stage the Veress needle is withdrawn, the wound enlarged with division of the linea alba and the 11·5 mm trocar cannula (used for the laparoscope) inserted using a drilling action with force applied from the wrist rather than the shoulder. It is important to stress that the sharp tip of the trocar should be kept parallel to the abdominal aorta. This is best achieved by lifting the abdominal wall below the trocar/cannula insertion site. As the trocar is hollow and has a hole near the tip, there is an easily audible hiss once the tip breaches the peritoneal membrane. At this point the trocar is withdrawn before the cannula is advanced further. There is no doubt that the insertion of the first trocar/cannula constitutes the most hazardous part of the operation and some surgeons opt for the open technique using a special cannula devised by Hasson. The risk of injury is reduced but not abolished by the use of disposable trocars/cannulae (AutoSuture, Ascot, UK or Ethicon, Edinburgh, UK) because of their spring-loaded sheaths. The telescope attached to the camera is then inserted and a laparoscopic inspection carried out to exclude unsuspected pathology including any injuries caused by the previous steps.

The remaining cannulae are then introduced under vision with complete safety using finger depression of the abdominal wall to identify the exact site of entry. The positions of the other cannulae are depicted in *Figure 1*. Most centres insert cannula 2 (11·5 mm) to the right of the midline to avoid the falciform ligament. This, however, causes 'crowding of the cannulae' and does not provide the ideal angle between the tips of two instruments (e.g. grasper and scissors) used simultaneously by the surgeon. The problem of entanglement with the falciform ligament is obviated by ensuring that the cannula is pushed in far enough to reach beyond the lower edge of the ligament. This cannula is used for a variety of 5 mm instruments within a reducing tube, and for the clip applicator. Cannula 3 (5·5 mm) is inserted in the

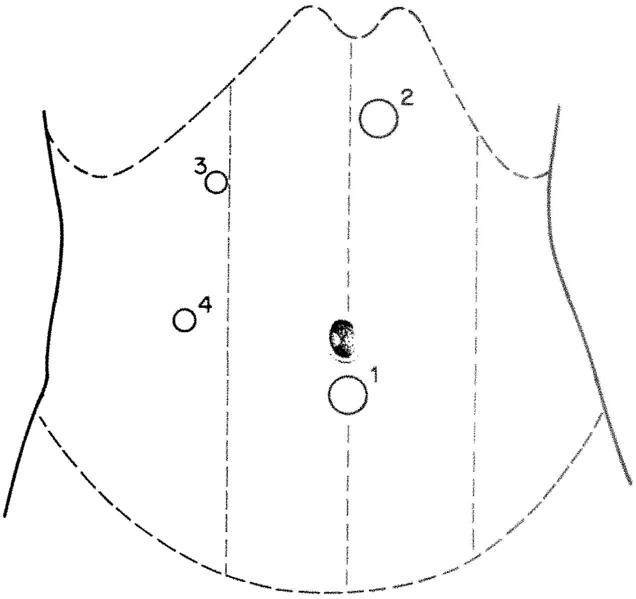

Figure 1 *Schematic representation of the position of the trocar/cannulae. Numbers 1 and 2 are 11·0 mm, the rest 5·5 mm*

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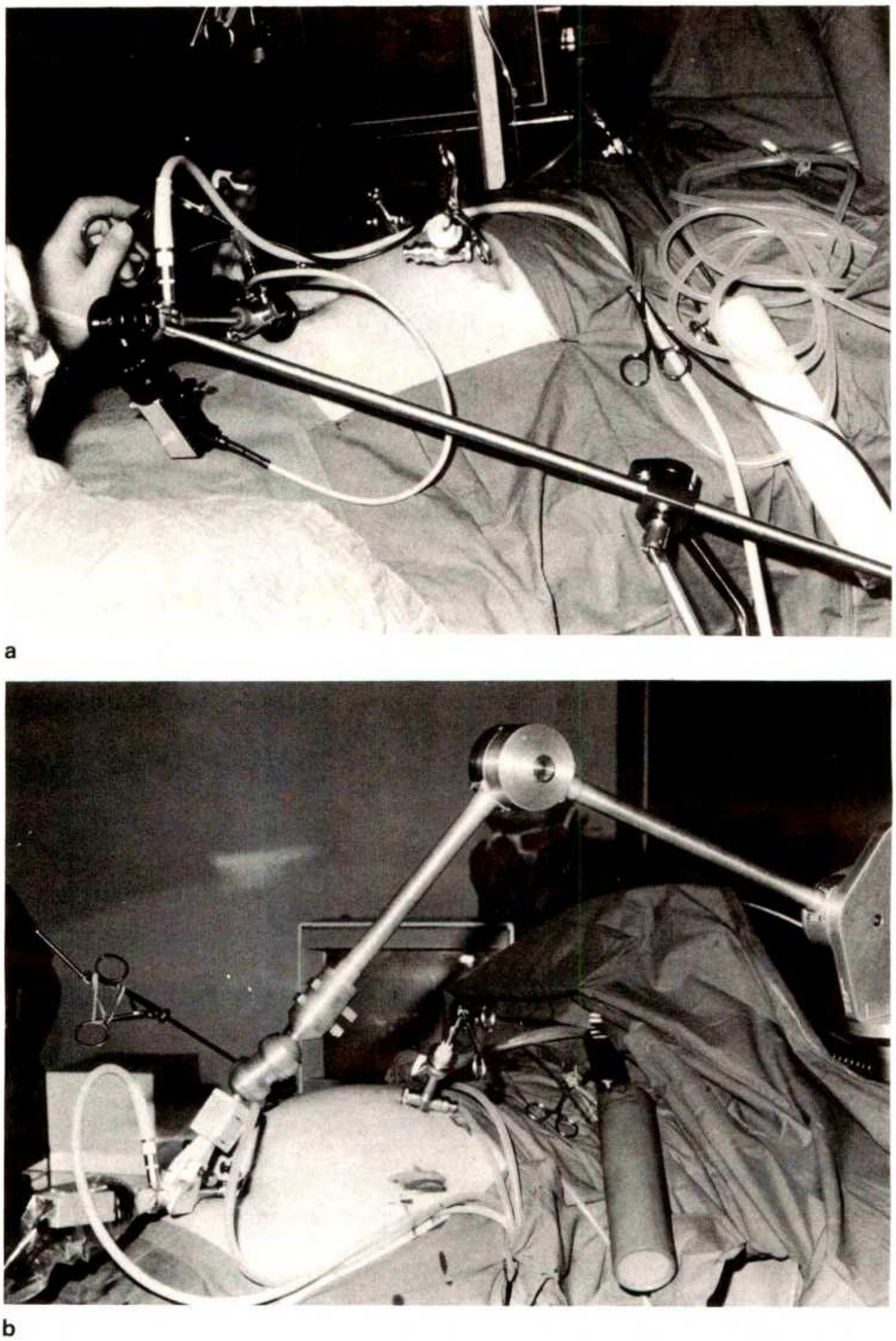

Figure 2 **a** *Laparoscope holder designed at Ninewells and based on the Omnitract universal joint;* **b** *vacuum-lock laparoscope holder. The sterile arm consists of 'shoulder', 'elbow' and 'wrist' joints which can be locked/unlocked by finger tip controls*

midclavicular line and is best sited over the fundus of the gallbladder and cannula 4 (5·5 mm, for the gallbladder grasper) should be placed well lateral in anterior axillary line and some 5·0 cm further distally so that it is almost at umbilical level.

Use of adjustable camera holder (Figure 2a)

This simple device developed at Ninewells dispenses with the need for a cameraman and permits the surgeon to adjust the telescopic field by unlocking one universal joint permitting both rotational and advancement/withdrawal movements. It avoids crowding of the operating environment and permits two-handed dissection by the surgeon. More recently we have been evaluating a vacuum-lock holder which has finger tip controls (First Assistant, Leonard Inc., Philadelphia). This undoubtedly is the ideal laparoscope holder (*Figure 2b*). It has been slightly modified (grasping head) from the original version introduced for operative arthroscopy.

Gallbladder retraction/endoretractor

In common with other centres, we consider that the best exposure of the angle of Calot is obtained by grasping the fundus of the gallbladder in a traumatic self-holding forceps and pushing the organ to the right and upwards. Lifting and turning the right lobe of the liver in this way exposes the cystic pedicle and common bile duct. However some 10 per cent of patients have a floppy quadrate lobe which obscures the field. In these patients the use of the endoretractor which fits on the 30° forward oblique telescope (used by us in preference to the forward viewing system) is invaluable for providing the necessary upward lift of the liver substance (*Figure 3*).

Dissection of the cystic pedicle

Unlike the vast majority of laparoscopic surgeons, we use the two-handed dissecting technique. The surgeon grasps the tissue exerting

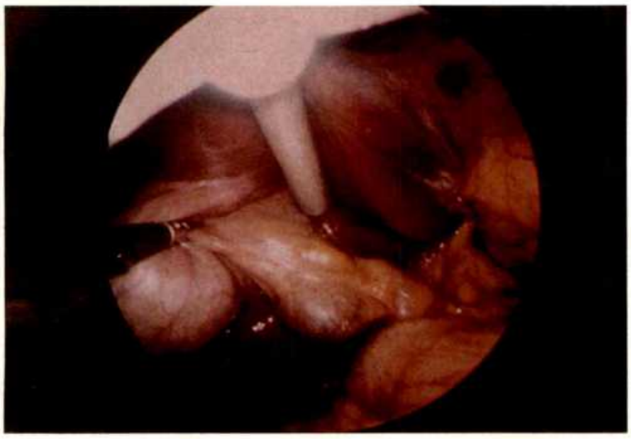

Figure 3 *Endoretractor used in association with the 30° forward oblique telescope*

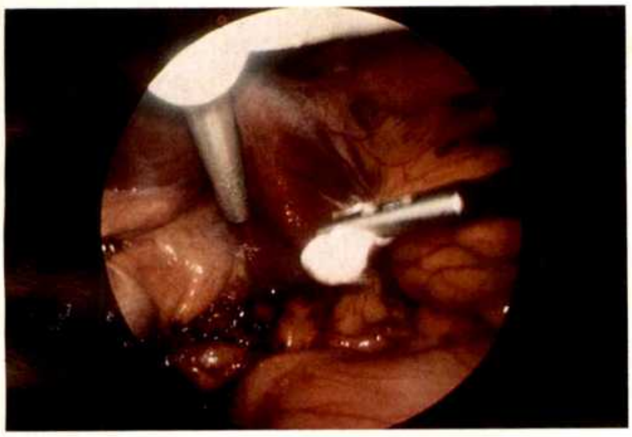

Figure 4 *Pledget swab dissection*

the correct tension with an atraumatic forceps held in his left hand whilst he dissects (preferably with twin action scissors) with the right hand. This is far preferable and safer than relying on the assistant to grasp and stretch the tissue while the surgeon dissects with the right hand. Both instruments are insulated (Storz, Tuttlingen, Germany). The principle entails the division of the superior peritoneal leaf of the cystic pedicle, the creation of windows between the cystic artery and duct and lifting the pedicle to review the anatomy from below and when necessary completing the dissection from behind. In difficult cases, particularly when Hartmann's pouch encroaches on the common duct and in patients with oozing or oedema, pledget swab dissection using the assembly shown in *Figure 4* is very useful and safe.

Dealing with cystic artery and duct

In the presence of normal anatomy, the cystic duct is dealt with first since ligature/division of the duct opens up the angle of Calot and provides better access to the cystic artery. However when the anatomy is abnormal (particularly in the presence of a looping right hepatic artery or anomalous origin of the right hepatic or common hepatic artery), clipping and division of the cystic artery is performed first. Although we prefer to clip the artery, our preference is to ligate in continuity the medial end of the cystic duct using dry chromic catgut and an external slip knot which is pushed down and accurately placed in accordance with the findings of the cholangiogram[6] (*Figure 5*).

Operative cholangiography

This is attempted routinely either through the gallbladder at the start of the procedure (first two cases) or through the cystic duct using the Olsen–Reddick cannula (Storz). The latter consists of a tubular cannula used for guiding the catheter (4 Fr) to the opened cystic duct and has two curved fenestrated jaws which are closed over the cystic duct once the catheter is *in situ*, thereby holding it in position and preventing leakage during injection of contrast (*Figure 6*).

Preliminary aspiration of the gallbladder

This is indicated if the gallbladder is tense as in the presence of a mucocele or resolving acute cholecystitis. Emptying the gallbladder allows the organ to be grasped and improves the exposure of the cystic pedicle.

Patients

A total of 61 patients was submitted to laparoscopic cholecystectomy. The patient details are shown in *Table 1*. All were elective procedures for symptomatic gallstones. Thirteen patients had a previous hospital admission for acute cholecystitis within 3 months of the operation. The preoperative investigations were standard liver function tests, ultrasound examination of the gallbladder and oral cholecystography. Single-dose antibiotic prophylaxis (cefuroxime) was administered after

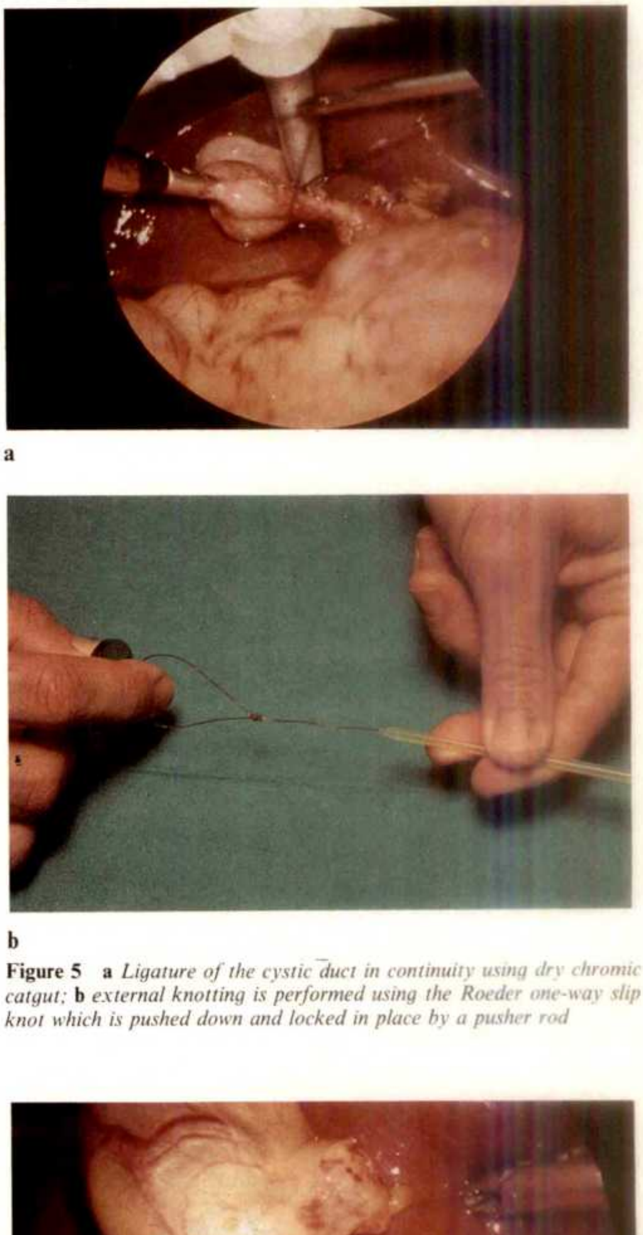

Figure 5 **a** *Ligature of the cystic duct in continuity using dry chromic catgut;* **b** *external knotting is performed using the Roeder one-way slip knot which is pushed down and locked in place by a pusher rod*

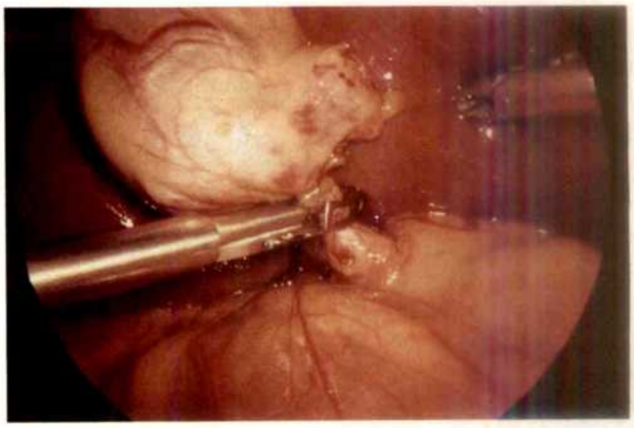

Figure 6 *Olsen–Reddick cannula with the jaws grasping the cystic duct after insertion of the cholangiography catheter*

Table 1 *Patient details*

Number of patients: 61 (49 women, 12 men)
Age: median 40 years (range 20–73 years)
Weight: median 73·5 kg (range 55–90 kg)
Gallstone disease:
  Previous biliary colic, $n = 60$
  Previous acute cholecystitis, $n = 13$*
  Existing acute cholecystitis, $n = 2$
  Mucocele, $n = 1$
  Somatostatin-induced stones†, $n = 1$

* Hospital admission; † acromegaly

induction of anaesthesia. Specific chemoprophylaxis against deep venous thrombosis was not used but graded compression stockings were worn by the patients routinely.

The median follow-up was 6 months, range 2–14 months.

Results

Intraoperative course

Conversion to open surgery. Laparoscopic cholecystectomy was completed in 60 patients. Elective conversion to open operation was undertaken in one patient (2 per cent) because a dilated bile duct and multiple calculi were found on the peroperative cholangiogram.

Complications during laparoscopic cholecystectomy. Bleeding was encountered in three patients. One resulted from a Veress needle stab involving the left mesocolon. The resulting haematoma was observed and confirmed to be static. Arterial bleeding from the posterior branch of the cystic artery was encountered in two patients. In both instances this complication was associated with early branching of the artery soon after its origin, the anterior branch being mistaken for the parent vessel. In both instances haemostasis was achieved by grasping the bleeding posterior branch until a clip was applied. The mean operative blood loss was 214 ml, range 0–700 ml. Three patients required transfusion (one during and two after operation).

The gallbladder was perforated or the lateral cystic clip/ligature dislodged with significant bile leakage in eight cases (13 per cent).

Cholangiography. Successful cannulation of the cystic duct was achieved in 53 of 59 cases (90 per cent). In the other two patients the cholangiogram was performed by gallbladder puncture. Cholangiography identified multiple unsuspected stones in a dilated bile duct in one patient (converted to open operation), a small ductal stone in another (managed by postoperative endoscopic papillotomy) and a duct anomaly (insertion of cystic duct into the right hepatic duct) in a further patient. The median time for a laparoscopic cholangiogram was 20 min, range 10–30 min.

Duration of operation. This was calculated from the time the patient was transferred to the operating table until completion and included the setting up time (approximately 15 min). The mean(s.d.) duration of the procedure in the series was 151·6(47·2) min (median 135, range 65–270 min). In patients with a non-functioning thickened/sclerotic gallbladder ($n = 10$), the mean(s.d.) total operating time was 180·5(43·8) min (median 175, range 110–270 min), as opposed to 132·3(49·27) min (median 120 min, range 65–210 min) for patients with a functioning organ.

Extraction of the gallbladder and stone load. The gallbladder was extracted through the umbilical wound with the cannula being retracted ahead of the organ. It was always possible to exteriorize the neck of the organ. All but 14 gallbladders had to be emptied of bile (by suction) and stones (by Desjardins forceps) before delivery through the parieties. One patient required enlargement of the subumbilical wound to enable extraction of a gallbladder containing a large calcified gallstone. Multiple gallstones (>5) were present in 33 organs, the mean(s.d.) stone size being 15(8·25) cm.

Postoperative course

Pain. Pain was experienced by the majority of patients and was of two types, either deep-seated right hypochondrial pain, or shoulder tip pain. Wound pain was abolished by local infiltration with 0·2 per cent bupivacaine at the end of the procedure. Analgesia was achieved with Omnopon (Omnopon, Roche, Welwyn Garden City, UK) administered intramuscularly as required. The median number of injections was 3 (range 1–8) and the median duration of opiate analgesic medication was 18 h (range 1–54 h).

Ileus. The index for this was taken as the time from the end of the operation until the patient was able to eat a solid meal, mean(s.d.) 24(15·4) h. In seven patients, the ileus was prolonged (36–72 h). There was no correlation between the technical difficulty, length of operation, bile leakage during surgery and duration of ileus. However, there was a significant positive correlation between the duration of ileus and the period of analgesic administration ($r = 0·76$, $P < 0·01$).

Morbidity. There were no deaths but there was one significant complication which required laparotomy (2 per cent). This patient developed pain in the right hypochondrium referred to the right shoulder and pyrexia on the third postoperative day. Ultrasound scanning demonstrated a subcapsular haematoma on the anterosuperior surface of the right lobe of the liver. This was confirmed at laparotomy when a 400 ml collection of semi-fluid blood associated with an instrumental stab wound was evacuated and drained. This was the third patient in the series and we would now deal with this complication by laparoscopy. This patient and one other patient who dropped her haemoglobin level by 2·0 g/dl over a 24-h period were transfused with 2 units of blood. Two patients complained of dysuria but their urine cultures were sterile. There have been no wound-related complications. Thus the total morbidity rate was 7 per cent.

Nausea/vomiting. These ailments were frequently experienced in the first 12 h and needed medication in 32 patients.

Hospital stay. The mean(s.d.) duration of hospital stay was 2·9(1·5) days (median 3, range 1–9 days).

Recovery. Forty-six patients answered a questionnaire inquiring about well-being and/or return to full activity or work after discharge. All but four are asymptomatic. The median time to full activity or return to work was 11 days, range 6–39 days. One patient was married 6 days after discharge and another undertook a transatlantic flight to attend a business meeting 5 days after leaving hospital.

Three patients have been readmitted (one to another hospital) with non-specific abdominal pain. Another patient developed diarrhoea and is under investigation.

Discussion

The initial experience with laparoscopic cholecystectomy has been most rewarding, particularly in terms of patient recovery and in the virtual abolition of wound-related complications. The procedure undoubtedly takes longer than open cholecystectomy, particularly in patients with a non-functioning gallbladder due to contraction of the cystic pedicle and enlargement of the cystic node rendering dissection in the triangle of Calot difficult.

Serious intraoperative and postoperative complications were infrequent. Early division of the cystic artery into anterior and posterior branches if not recognized can lead to bleeding as the anterior branch is mistaken for the parent artery. This is an important practical consideration as control of active arterial bleeding is difficult during laparoscopic surgery since the cut vessel retracts within adjacent tissues and fat. Perforation of the gallbladder is a fairly frequent occurrence but does not appear to influence outcome provided the gutters are irrigated and aspirated at the end of the procedure.

The use of an adjustable laparoscope holder greatly facilitates the conduct of the procedure and, by obviating the need for a cameraman, allows more elbow room around the operating table. The significant correlation between the duration of ileus and period of analgesic medication is interesting and suggests a drug-induced delay in recovery of gastrointestinal function after laparoscopic surgery.

Aside from training implications which on a national scale will impose logistic problems and which need to be addressed, the development of minimal access surgery will require more operating time and ideally purpose-designed operating theatres. There are, in addition, several unresolved issues. These include the exact contraindications to laparoscopic cholecystectomy, the ideal dissection technique and the need or otherwise for routine peroperative cholangiography. French surgeons perform preoperative infusion cholangiography with tomography to exclude ductal calculi and use peroperative cholangiography selectively in suspect cases[1–3]. Unquestionably, this practice saves operating time and the experience reported from Bordeaux and Paris is favourable with no adverse contrast reactions and good quality imaging of the common bile duct. None the less, an operative cholangiogram gives additional information concerning the precise anatomy of the extrahepatic biliary tract, information which is important in influencing where the cystic duct is clipped or ligated. Only prospective studies will resolve these issues.

We do not use nor advocate the use of lasers (Nd-YAG or KTP) for laparoscopic cholecystectomy. Although elegant and efficient, there are certain important disadvantages to the use of laser thermal probes for this procedure. In the first instance they impose an extra hazard and lead to further congestion of the operating room already packed with bulky high technology equipment. With a KTP laser (which is produced by frequency doubling Nd-YAG with potassium titanyl phosphate crystal), the visible green light 'scatters' during activation and virtually blots out vision. As the output of an Nd-YAG laser is invisible, it is free of this disadvantage. However, both lasers are liable to cause the 'shoot-past' or 'past-pointing' phenomenon due to imperfect beam collimation and misdirections of beam caused by even the slightest tremor, so that light energy is delivered on and beyond the intended target, making bile duct, portal vein, hepatic artery and vena caval injuries a real hazard. Indeed these injuries, though rare, have been encountered in some cases with a fatal outcome. There is a further theoretical disadvantage with the KTP system since its wavelength (530 nm) photoactivates haemoglobin and its derivatives with the generation of reactive species which are highly toxic. This may be more important than is currently realized, particularly as the carbon dioxide used for insufflation induces vasodilatation of the subserosal vessels. The risk of widespread adhesion formation is a possibility and needs to be excluded before green light is delivered in prolonged pulses inside the peritoneal cavity at relatively high energy levels (10–12 W).

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Reduced postoperative hospitalization after laparoscopic cholecystectomy

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An initial experience of laparoscopic cholecystectomy in 50 consecutive patients was reviewed and the results compared with those of a group of 25 patients who underwent laparotomy cholecystectomy during the 3 months before the introduction of laparoscopic cholecystectomy. Laparoscopic cholecystectomy was successfully performed in 44 of 50 consecutive patients in whom it was attempted. When compared with laparotomy, laparoscopy cholecystectomy was associated with longer mean(s.d.) anaesthesia, 155(61) min versus *102(31) min* ($P<0{\cdot}001$), *shorter mean postoperative hospital stay, 3·5(1·5)* versus *8·8(3·2) days* ($P<0{\cdot}001$), *and reduced mean cost, £895(376)* versus *£2210(822)* ($P<0{\cdot}001$). *Perioperative morbidity was also reduced following laparoscopy cholecystectomy (9 per cent* versus *16 per cent) but not significantly so. Laparoscopic cholecystectomy is a safe, effective procedure which completely removes the gallbladder. It significantly reduces hospital stay, is cosmetically satisfactory and has financial benefits. We suggest that this technique be considered for all patients having cholecystectomy.*

In 1882 Langenbuch performed the first cholecystectomy[1] and it is still the standard surgical method for dealing with the diseased gallbladder. Alternative treatments for gallstones have been advocated recently including stone dissolution, lithotripsy and percutaneous stone removal. All of these approaches, however, leave the gallbladder *in situ* with the possibility of stone recurrence. The development of minimally invasive techniques in urology[2] and gastroenterology[3] has stimulated general surgeons to explore the therapeutic potential of laparoscopy in the management of gallbladder disease. Laparoscopic cholecystectomy is a feasible and safe procedure which is now being performed regularly in a number of centres[4–10]. We reviewed our initial experience with laparoscopic cholecystectomy in our first 50 consecutive patients and compared the results with a group of 25 patients who underwent laparotomy cholecystectomy during the 3 months before the introduction of laparoscopic cholecystectomy.

Patients and methods

The hospital records of all patients who underwent cholecystectomy at Beaumont Hospital between November 1989 and July 1990 were reviewed. Twenty-five patients had laparotomy cholecystectomy between November 1989 and February 1990 and 50 had laparoscopic cholecystectomy between February and July 1990. The patients ranged in age from 17 to 85 years with a mean(s.d) of 48(14) years Sixteen patients were men and 59 were women. The two groups were comparable in terms of mean(s.d.) age, 51(14) *versus* 46(13) years, percentage of patients who were male, 24 *versus* 21 per cent, mean weight, 67(12) *versus* 65(11) kg, and American Society of Anesthesiologists (ASA) status before operation.

Biliary colic, chronic cholecystitis, acute cholecystitis, gallstone pancreatitis and empyema of the gallbladder were the indications for cholecystectomy and were evenly distributed between the two groups (*Table 1*). One patient in the laparotomy group had cholesterolisis of the gallbladder while one patient in the laparoscopy group had a gallbladder polyp Patients who were jaundiced were excluded from the analysis However, one patient who had been jaundiced underwent endoscopic retrograde cholangiopancreatography (ERCP) and duct clearance before laparoscopic cholecystectomy.

Anaesthesia time, morbidity, postoperative hospital stay and cost were recorded. The estimated cost of maintaining a patient in Beaumont Hospital for one day is £250.00. All of the following results are expressed as mean(s.d.). Statistical analyses were performed using Student's *t* test for unpaired observations for age, weight, anaesthesia time, postoperative hospital stay and cost The χ^2 test was used for comparison of percentages.

Operative technique

All patients received prophylactic antibiotics and subcutaneous heparin during the perioperative period. Laparotomy cholecystectomy was performed under general anaesthesia via a right subcostal incision. Peroperative cholangiography was performed in all the laparotomy patients and all had a small suction drain placed at the end of the operation.

Laparoscopic cholecystectomy, which is performed by two surgeons and one assistant, requires general anaesthesia with endotracheal intubation. The patient is placed in the lithotomy position with the feet down. A nasogastric tube is passed to decompress the stomach and the patient is rotated slightly to the left A Veress needle is inserted into the midline just below the umbilicus and approximately 5000 ml carbon dioxide is insufflated into the peritoneal cavity to maintain a pressure of approximately 15 mmHg. The Veress needle is replaced by a 10 mm trocar and sheath through which is passed a 25° laparoscope which is attached to a video camera. The rest of the procedure is performed by video dissection displayed on a television monitor. After a full laparoscopic examination of the abdomen a second 5 mm trocar is inserted to the right of the midline and the falciform ligament at the level of the xiphisternum. Through this a rod, which doubles as a suction catheter, is placed to act as a liver edge retractor. A gallbladder grasping forceps is placed through another 10 mm trocar in the right iliac fossa while a large 11 mm operating trocar is positioned to the left of the umbilicus

Table 1 *The indications for cholecystectomy*

	Cholecystectomy		
	Laparotomy ($n=25$)	Laparoscopy ($n=50$)	Total ($n=75$)
Biliary colic	5 (20)	16 (32)	21 (28)
Chronic cholecystitis	9 (36)	17 (34)	26 (35)
Acute cholecystitis	6 (24)	7 (14)	13 (17)
Gallstone pancreatitis	4 (16)	5 (10)	9 (12)
Gallbladder empyema	0 (0)	4 (8)	4 (5)
Other	1 (4)	1 (2)	2 (3)

Values in parentheses are percentages

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Table 2 *Complications of cholecystectomy*

	Cholecystectomy		
	Laparotomy ($n=25$)	Laparoscopy ($n=44$)	Total ($n=69$)
Pulmonary embolism	1 (4)	0 (0)	1 (1)
Urinary tract infection	3 (12)	0 (0)	3 (4)
Atelectasis	1 (4)	0 (0)	1 (1)
Jejunal perforation	0 (0)	1 (2)	1 (1)
Bile leak	0 (0)	2 (5)	2 (3)
Jaundice	0 (0)	1 (2)	1 (1)
Total no. of patients with complications	4 (16)*	4 (9)	8 (12)

Values in parentheses are percentages. * One patient developed both pulmonary embolism and urinary tract infection

Table 3 *Details of the six patients in whom laparoscopic cholecystectomy was unsuccessful*

Sex	Age (years)	Indication	Reason for failure
M	72	Empyema	Unable to grasp tense gallbladder
F	50	Empyema	Very inflamed gallbladder
F	30	Empyema	Clip applicator failure
F	72	Acute	Unable to identify anatomy safely
F	38	Acute	Unable to identify anatomy safely
F	40	Chronic	Bleeding from gallbladder bed

The fundus of the gallbladder is grasped and pulled gently to the right while the liver edge is retracted and pulled to the left. This manoeuvre exposes Calot's triangle and by a combination of blunt and sharp dissection using a diathermy scissors, the cystic duct and artery are exposed The exposed artery and duct are divided between clips Using electrocautery the gallbladder is dissected from the gallbladder bed and removed via the 10 mm port in the right iliac fossa. We remove the gallbladder via this port in preference to the subumbilical route as the shutter valve effect of the abdominal muscles in the right iliac fossa obviates the need to place a suture in the abdominal wall after the gallbladder has been removed. If a large stone is encountered the gallbladder neck can be delivered on to the skin, opened and the stone crushed by an instrument placed inside the gallbladder. The gallbladder bed is inspected and irrigated with saline and if necessary a drain may be placed.

Results

There was no death in either group. Of the 25 patients who underwent laparotomy cholecystectomy four (16 per cent) developed a serious complication (*Table 2*). An 85-year-old woman with gallstone pancreatitis developed a pulmonary embolism and a urinary tract infection. Two other patients had urinary tract infections while a single patient had atelectasis. Minor complications included superficial wound infection, wound pain, skin rash and oesophagitis. Two patients who required choledochotomy for unsuspected common bile duct stones had uneventful recoveries.

Laparoscopic cholecystectomy was successful in 44 (88 per cent) of the 50 patients in whom it was attempted. Details of the patients in whom it was not successful are given in *Table 3*. Three of these patients had an empyema of the gallbladder, two of which were tense, inflamed and impossible to hold with a grasping forceps even after attempts at gallbladder aspiration. The procedure was abandoned in the third patient because of failure of the clip applicator. The anatomy could not be clearly demonstrated in two patients with acute cholecystitis and a single patient with chronic cholecystitis required immediate laparotomy for bleeding from the gallbladder bed.

Of the remaining 44 patients who underwent laparoscopic cholecystectomy, four (9 per cent) had a serious complication (*Table 2*). One patient who sustained a jejunal perforation from the Veress needle underwent laparotomy for peritonitis 2 days after the procedure. She was discharged home, well, 6 days later. Two patients who underwent laparoscopic cholecystectomy for acute cholecystitis and empyema of the gallbladder respectively had prolonged biliary drainage from suction drains placed at the time of the procedure. Drainage resolved spontaneously in both patients and they were discharged after 6 and 8 days respectively. The fourth patient returned 14 days after cholecystectomy with jaundice from common bile duct stones and underwent endoscopic sphincterotomy and duct clearance without problem. Minor complications included upper abdominal pain in five patients and superficial infection at the umbilical wound in two.

Comparison of anaesthesia time, postoperative hospital stay and cost is given in *Table 4*. Anaesthesia time was significantly longer in patients undergoing laparoscopic cholecystectomy However, with increasing experience this has decreased and was 115(49) min for our last ten patients. Laparoscopy cholecystectomy, either attempted or successful, was associated with significant reductions in both hospital stay and cost.

Discussion

To date approximately 325 laparoscopic cholecystectomies have been reported in the literature with no death, minimal morbidity and a success rate of 98 per cent[6–10]. Previous authors have been very selective in the patients to whom they offered laparoscopic cholecystectomy, excluding those with acute cholecystitis, gallstone pancreatitis, thickening of the gallbladder on ultrasonography, and jaundice. In contrast we have offered laparoscopic cholecystectomy to all of our patients with the exception of those with jaundice. This probably accounts for the success rate of 88 per cent; five of the six patients in whom laparoscopic cholecystectomy failed had empyema of the gallbladder or acute cholecystitis.

We did two laparotomies for complications of the procedure; one immediately for bleeding and one at 48 h for peritonitis from a jejunal perforation caused by the Veress needle. Dubois and colleagues also did two laparotomies for complications after 220 laparoscopic cholecystomies; one for bleeding from the cystic artery and one for a subhepatic collection detected 48 days after the procedure[7]. Coleman *et al.* in a series of 50 patients did only one laparotomy for iatrogenic bile leakage[9]. Perissat[10] and Reddick[6] observed no complications in 25 patients each after laparoscopic cholecystectomy.

Early discharge following laparoscopic cholecystectomy was also reported by Reddick[6] His patients were discharged at a mean of 1·96 days after the procedure compared with 2·8 days for a concurrent group of 25 patients who had mini-laparotomy cholecystectomy. We observed a more significant decrease in postoperative hospital stay following laparoscopic cholecystectomy, but this was in comparison with standard laparotomy cholecystectomy The most dramatic finding in Reddick's study,

Table 4 *Comparison of anaesthesia time, hospital stay and cost in patients undergoing laparotomy and laparoscopy cholecystectomy*

	Cholecystectomy		
	Laparotomy (all) ($n=25$)	Laparoscopy (successful) ($n=44$)	Laparoscopy (attempted) ($n=50$)
Mean(s.d) anaesthesia time (min)	102(31)	155(61)	154(59)*
Mean(s.d.) postoperative hospital stay (days)	8·8(3·2)	3·5(1·5)*	4·2(2·1)*
Mean(s.d.) cost (£)	2210(822)	895(376)	1040(534)*

* $P<0·001$ *versus* laparotomy cholecystectomy group

however, was that after laparoscopic cholecystectomy patients returned to work after a mean of 6·5 days, compared with 34 days after mini-laparotomy[6].

The management of patients with possible common bile duct stones is controversial. We excluded patients who were jaundiced but undertook laparoscopic cholecystectomy in five who presented with gallstone pancreatitis and recommend that this group have ERCP before surgery. One patient who had been jaundiced had ERCP and sphincterotomy before laparoscopic cholecystectomy while a second patient subsequently required endoscopic sphincterotomy. Although peroperative cholangiography is feasible in 75 per cent of patients undergoing laparoscopic cholecystectomy[6], we have not performed it because we would not undertake a surgical exploration of the common bile duct even if the cholangiogram demonstrated common bile duct stones. Many stones pass spontaneously into the duodenum[11] or could be more easily dealt with by ERCP and sphincterotomy. However, the best way of treating this problem remains to be determined.

The advantages of laparoscopic cholecystectomy are several. Firstly, the diseased gallbladder is removed. There is no large incision, only three small stab wounds in the abdomen and a 1 cm incision in the umbilicus Technically, dissection of the cystic artery and duct is very precise and bleeding from the gallbladder bed is easily controlled. Postoperative pain is reduced[9] and the cosmetic advantage is obvious. There is no risk of wound dehiscence. The present analysis has demonstrated a significant financial saving using the procedure. The patient is discharged from hospital quickly and can return to work after 1 week[6]. Thus, there are economic advantages to the patient, his community and the healthcare provider.

The only disadvantage to laparoscopic cholecystectomy is that operating time is longer than for mini-cholecystectomy[6] or for standard cholecystectomy. However, with more experience operating time decreases. There is also a learning curve with the procedure which may be difficult in patients with an acute cholecystitis. We suggest that laparoscopic cholecystectomy should be considered in all patients undergoing cholecystectomy.

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Piezoelectric lithotripsy for gallstones: analysis of results in patients with extended selection

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Extracorporeal shock wave lithotripsy (ESWL) is successful in fragmenting gallstones, but <28 per cent of patients with gallstone disease fulfil the conventional criteria for treatment. However, no data exist to substantiate these selection criteria. In this study, the selection criteria were broadened to include patients with radiolucent stones of any size and number, and radio-opaque stones <3 cm in diameter. To date, 108 symptomatic patients with gallstones have received treatment. All patients received up to six outpatient sessions of ESWL (6000 shock waves per session) without sedation or analgesia. The dissolution therapy consisted of combined bile salt and terpene administration. The clearance rates were 9 per cent within 2 months, 21 per cent at 2–4 months, 38 per cent at 4–8 months, 60 per cent at 8–12 months, and 78 per cent at 12–18 months. Of patients with a successful outcome only 19 (18 per cent) would have satisfied traditional selection criteria. There have been no significant complications except in one patient who developed mild acute pancreatitis, which settled on conservative treatment, and two patients who developed acute cholecystitis. This study would suggest that the previously accepted selection criteria underestimate the number of patients suitable for gallstone ESWL and dissolution therapy.

The introduction of extracorporeal shock wave lithotripsy (ESWL) has revolutionized the treatment of kidney stones[1]. Early results indicate that it is also possible to shatter gallstones and ultimately produce complete gallbladder clearance when lithotripsy is combined with bile salt therapy[2–4]. Clearly, this form of therapy has many attractions as it avoids the need for surgery and general anaesthesia and may be performed as an outpatient procedure[3]. Encouraging results have been reported by a number of authors, but the selection criteria for gallstone lithotripsy are arbitrary and appear to be based on those that have become established for bile salt therapy alone[5,6]. Although this form of therapy requires a functioning gallbladder, the physical characteristics of the gallstones selected for treatment are open to question. The stone characteristics defined by Sackmann *et al.* for inclusion in their study include solitary radiolucent stones with a diameter of up to 30 mm, or up to three radiolucent stones with a similar total stone mass[2,5,7].

Such strict criteria may reduce the number of patients suitable for this type of therapy and therefore limit its potential in management[7]. We have used the combination of lithotripsy and oral dissolution therapy for gallstone clearance since August 1987. To extend the application of this treatment we have broadened our criteria to include a wider range of gallstone morphology than has been previously suggested and we report our experience to date.

Patients and methods

We have treated 124 patients (29 men, 95 women) of mean age 43 years (range 11–81 years) between August 1987 and June 1989. Patients were selected if they met our extended selection criteria[3], these criteria are shown in *Table 1* with the conventional selection criteria described by Sackmann *et al.*[2]

All patients had suffered one or more attack of biliary colic. We did not consider lithotripsy if patients were pregnant, had documented peptic ulcer disease, had haematological disorders or were on anticoagulant therapy, or if they had suffered complications of gallstones (including evidence of jaundice or bile duct stones, acute cholangitis, acute pancreatitis or acute cholecystitis).

Sixteen patients were excluded from the study, leaving 108 for assessment. Of those excluded, four failed to return after the first treatment, two patients have emigrated, four patients did not tolerate bile acid therapy and two became pregnant. In the remaining four, lithotripsy was abandoned because of difficulty in visualization of the gallbladder with the integral ultrasound transducer probe when the patient was lying prone.

All patients underwent a full clinical assessment and full blood count and liver function tests were performed. Radiological investigations included oral cholecystography, abdominal ultrasound and plain film of the abdomen to assess gallstone calcification.

Shock wave therapy

Lithotripsy was carried out using the EDAP LT-01 lithotripter (Exploration Development des Application de la Physique, Marne la Vallée, France) which employs a piezoelectric system in which shock waves are generated from 320 ceramic crystals. This system[8] has a focal area of approximately 2.3 × 23 mm, a peak pressure at the focal region of 1031 atm and a rise time of 44 ns. All treatments were carried out as an outpatient procedure and patients were instructed to fast from midnight the night before. The gallbladder was initially localized by a hand-held ultrasound probe before placing the patient in the prone position on a fluid-filled dome within a custom-designed table. Contained within this dome is the main ultrasound mechanism used to

Table 1 *Selection criteria for gallstone lithotripsy*

	Conventional	Dublin
Symptomatic gallstones	Yes	Yes
Functioning gallbladder	Yes	Yes
Size	<3 cm	Any
Number	<3	Any
Calcification	No	Yes <3 cm

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focus the beam of shock waves onto the target gallstones within the gallbladder Continuous real-time ultrasound monitoring ensured that the ESWL beam remained on target during the course of treatment. Each patient received 6000 shock waves per treatment session up to a maximum of six treatments at 1–4-weekly intervals. The endpoint of lithotripsy was to achieve gallstone fragment sizes of <4 mm diameter. The shock waves were administered at a frequency of 2·5 waves/s and 100 per cent power. This setting was chosen based on previous *in vitro* and animal studies performed by our group[9,10]. None of the patients studied required any analgesia or sedation, thus allowing them to return to their normal daily activity after treatment.

Dissolution therapy

To promote clearance of gallstone fragments from the gallbladder after ESWL, all patients received combination dissolution therapy consisting of, approximately, 7 mg/kg per day chenodeoxycholic acid and 7 mg/kg per day ursodeoxycholic acid. The two bile acids were administered in a single tablet form (Lithofalk®, Dr Falk GmbH and Company, Freiburg, Germany)[6,11–13]. In addition patients were given Rowachol® (Rowa Pharmaceuticals Ltd., Cork, Ireland) one tablet three times a day. This agent contains a mixture of terpenes, including menthol, which, when administered in conjunction with the bile salt therapy, enhances its cholelitholytic effect[14–16] In addition, terpenes have an antispasmodic action and it was felt that their administration might reduce episodes of biliary colic[14]. Adjuvant treatment was started 1 week before the first ESWL session and continued throughout the period of follow-up until complete clearance of the fragments, and then for a further 3 months to ensure clearance

Postlithotripsy follow-up

All patients were followed monthly by clinical and ultrasonographic assessment. Two consecutive ultrasound examinations at a month's interval, and an oral cholecystogram, were required to establish total gallstone clearance. Time to clearance was measured from the date on which the first lithotripsy treatment was administered.

We classified patients into four groups· those who achieved 100 per cent gallstone clearance; those with >50 per cent clearance, that is, fragmentation with significant clearance of the gallstone mass; those with <50 per cent clearance, that is, fragmentation with insignificant clearance of the gallstone mass; and those with no clearance (*Table 2*).

Failure was defined as insignificant fragmentation or clearance of fragments after a maximum of six treatment sessions and follow-up of 6 months, or the development of gallstone complications. In the failure groups, 14 patients have undergone cholecystectomy and all the stones or fragments harvested were analysed for chemical composition by X-ray diffraction and infrared spectroscopy (Calculab, Richmond, Virginia, USA). The percentage of cholesterol and calcium bilirubinate was determined in both stone interior and exterior (*Table 3*).

Statistical analysis was performed using the χ^2 test

Results

Shock wave treatment was performed on 108 patients at a total of 335 treatment sessions, each patient requiring an average of three treatments (range 1–6 treatments) at an average of 2-weekly intervals (range 1–4 weeks). Their mean duration of follow-up was 6 months (range 1–20 months). The stone profiles of the patients studied together with the outcome of treatment to date are summarized in *Table 2*. Forty-one patients had solitary stones and the remaining patients had multiple stones. Eighteen patients had calcified stones on plain film of the abdomen. Of the 108 patients, 67 would not have been deemed suitable on the basis of conventional criteria (*Table 1*). The results of treatment were as follows.

Clearance 100 per cent 49 patients achieved total gallbladder clearance with a mean follow-up of 6·2 months (range 1–18 months). Only 19 of these patients would have been deemed suitable according to conventional criteria.

Clearance >50 per cent· 30 patients have had >50 per cent reduction in stone mass with a mean follow-up of 6·7 months (range 1–18 months). Only 13 of these patients would have been suitable according to conventional criteria.

Clearance <50 per cent. 11 patients have had <50 per cent reduction in gallstone mass. Only three of these patients would have been considered suitable by conventional criteria. The mean duration of follow-up of these patients is short at 3·7 months (range 1–6 months).

Table 2 *Clearance of gallstones based on stone profile*

No. of stones	Size (cm)	Gallstone clearance			
		100%	>50%	<50%	0
Lucent					
1	<1	3	3	1	–
	2–3	13	5	1	2
	3–5	–	3*	–	2*
2,3	<1	4	2	2	–
	2–3	1	3	–	1
>3	<1	21*	10*	4*	4*
	2–3	2*	1*	–	2*
Opaque					
1	<1	1*	–	–	
	2–3	1*	2*	–	4*
2,3	2–3	1*	–	–	–
>3	<1	1*	1*	1*	2*
	2–3	1*	–	2*	1*
Total		49	30	11	18

* Unsuitable according to conventional criteria

Clearance 0 per cent: 18 patients were considered to be treatment failures, and to date 14 have had cholecystectomy. We have analysed the treatment failures in detail as summarized in *Table 3*. Nine of these patients had solitary stones and we could not achieve stone fragmentation in eight of those. Also, the majority of these solitaires were large (approximately 3 cm in diameter) and five were radio opaque on plain film of the abdomen.

In contrast to the patients with solitaires, patients who failed treatment and had multiple stones usually achieved fragmentation but these fragments did not clear after 6 months of dissolution therapy.

Although two patients in the failure group had faint opacification of their gallbladders, there seemed to be no correlation between intensity of gallbladder concentration on oral cholecystogram and successful gallbladder stone clearance. Indeed, three of the patients in the 100 per cent clearance group had faint opacification and yet had successful clearance.

In relation to stone content there was no significant difference in the chemical composition of gallstones that did not fragment and gallstones that fragmented but failed to clear. In addition, the majority of the stones were of mixed composition with a high concentration of calcium bilirubinate in both stone surface and core.

Seven patients in the failure group had calcified stones and these varied from stones with core calcification ($n=5$) to stones with calcified shells ($n=2$). Fragmentation could not be achieved in five of these patients with calcified stones and in the remaining two the fragments failed to clear after lithotripsy. However, five of the patients who achieved complete clearance of their gallstones had radio-opaque stones at the time of entry into the study.

Four patients were considered to be treatment failures of ESWL because of complications. Of these, two developed acute cholecystitis, one acute pancreatitis, and one became jaundiced. All of these patients underwent cholecystectomy and histological examination of the gallbladders showed acute inflammatory changes or evidence of chronic cholecystitis but no evidence of specific lithotripsy-induced injuries.

Stone free rate

Taking all patients examined within 2 months of the first lithotripsy session, 9 per cent were completely stone free. Similarly, 21 per cent were tone free at 2–4 months, 38 per cent at 4–8 months, 60 per cent at 8–12 months, and 78 per cent

Table 3 *Analysis of the stones that failed to respond to lithotripsy and oral dissolution therapy*

	Stone characteristics					Chemical composition (%)			
						Exterior		Interior	
Patient	Number	Size (cm)	Opaque	Gallbladder opacification†	Cause of failure	‡CHO	CaBil	CHO	CaBil
1	1	3	No	Moderate	No fragmentation	80	20	80	20
2	1	3	No	Moderate	No fragmentation	10	80	95	5
3*	1	2	Yes	Faint	No fragmentation	–	–	–	–
4*	1	3	No	Moderate	No fragmentation	–	–	–	–
5	1	2·8	Yes	Moderate	No fragmentation	40	20	10	90
6	1	3·5	Yes	Moderate	No fragmentation	65	35	85	15
7	1	4·5	Yes	Moderate	No fragmentation	50	50	50	50
8	1	2·9	Yes	Moderate	No fragmentation	30	70	70	30
9	2	3·0	No	Moderate	No fragmentation	75	25	20	80
10	>20	0·7	Yes	Good	No clearance	2	98	95	5
11*	>30	0·6	No	Good	No clearance	–	–	–	–
12	>3	1·0	No	Moderate	No clearance	40	40	50	50
13*	>20	0·5	No	Good	No clearance	–	–	–	–
14	>10	1	No	Faint	No clearance	25	75	50	50
15	>10	1	No	Good	Jaundice	85	15	5	95
16	>3	1·5	Yes	Moderate	Cholecystitis	50	30	50	30
17	1	4·0	No	Moderate	Cholecystitis	70	30	95	5
18	>3	2·0	No	Moderate	Pancreatitis	70	30	70	30

* Have not had cholecystectomy; † on oral cholecystogram; ‡ CHO, cholesterol; CaBil, calcium bilirubinate

Table 4 *Stone free rate according to the selection criteria employed*

	Period of observation (months)				
	0–2 months	2–4 months	4–8 months	8–12 months	12–18 months
Suitable by conventional criteria	7/36 (19)	12/36 (33)	13/29 (45)	11/19 (58)	5/6 (83)
Unsuitable by conventional criteria	3/69 (4)	9/63 (14)	14/47 (30)	18/29 (62)	9/12 (75)
All patients (Dublin criteria)	10/108 (9)	21/100 (21)	27/72 (38)	29/48 (60)	14/18 (78)

Values given are no of patients free of stones/no. of patients seen at follow-up (percentage)

at 12–18 months (*Table 4*). We compared the results achieved in patients with a stone profile compatible with the conventional criteria ($n=36$) with those of patients with a stone profile unsuitable for treatment according to the conventional criteria ($n=69$). The number of patients clear of gallstones in the former group was significantly higher than in the latter group at 0–2 months (7 of 36 *versus* 3 of 69, $P<0{\cdot}05$), and at 2–4 months (12 of 36 *versus* 9 of 63, $P<0{\cdot}05$) (*Table 4*).

Lithotripsy was well tolerated by the majority of the patients undergoing treatment. Three patients were unable to maintain their position on the table for more than 20 min because of back pain. Fifteen patients (14 per cent) complained of right upper quadrant discomfort after treatment, but this settled spontaneously and required no analgesia. None had any evidence of skin ecchymosis or haematuria. Fourteen patients (13 per cent) suffered an attack of biliarycolic during follow-up

Recurrence

Follow-up radiological examination of the patients with total gallstone clearance revealed recurrent stones in four of 49 patients within 7–11 months (mean 8 months after clearance). The recurrent stones were all multiple with a mean diameter of 5 mm. In one case the stones recurred during pregnancy and the patient was not treated; in two patients dissolution therapy cleared the recurrent stone; and the fourth patient refused further therapy. The stones were symptomatic in two of the four patients.

Discussion

There are currently several different lithotripters available and these machines often have very different specifications. Because the energy source of the shock wave and their focusing systems differ, the resulting shock waves have different characteristics with each lithotripter. The EDAP LT-01 has a small focal point where the shock waves strike the target and, although this necessitates accurate localization, less pain is produced and the potential for tissue damage to surrounding structures is reduced[17]. Before undertaking clinical studies we have previously determined the safety limits of the EDAP LT-01 system and have found that 6000 shock waves per treatment session is both safe and effective in fragmenting gallstones[9,10]

Initial studies from Munich, using ESWL fragmentation and dissolution therapy for gallstone clearance, have been very encouraging[2]. It is reasonable to suggest that this group initially selected patients for treatment who might have the best chance of success, as is often the case in the early assessment of a new technique. Thus, > 70 per cent of the patient population referred to them were considered unsuitable for this form of treatment, and in many cases this was because of the gallstone characteristics.

By extending the selection criteria, as in the present study, we calculated that we would include up to 60 per cent of patients who might otherwise be treated by cholecystectomy.

Although this is an early report of an on-going study, we already have evidence to show that it is possible to extend the scope of ESWL and dissolution therapy for gallstones. Over half of our patients who have achieved total clearance would not have been deemed suitable according to the Munich criteria. Of particular note has been the success rate achieved in patients with more than three stones. Forty per cent of our patients who have achieved complete clearance had more then three stones. We have also achieved some success with calcified stones. Five patients have achieved complete clearance; two of these had stones with calcification in the shell and the other three had calcification in the nucleus. However, seven patients with calcified stones were deemed to be treatment failures, as their stones did not fragment, although two of these stones were >3 cm in diameter.

With regard to stone size, the great majority of stones in our patients were <3 cm in diameter. However, eight patients had larger stones and successful fragmentation was achieved in four. However, none has yet reached the stage of complete gallbladder clearance of their fragments. Our approach of repeated lithotripsy to deal with larger fragments may yet prove beneficial in this group.

The clearance rates reported by Sackmann *et al.*[2] are better than those in the present study. When comparing the stone free rate of patients with stone profile similar to those employed by the Munich group the results are comparable. However, we anticipate that the long-term future of ESWL will to a large extent depend on its ability to treat a greater percentage of gallstone sufferers than the Munich group.

We have previously shown that adjuvant dissolution therapy is a critical addition to ESWL in the treatment of gallstones[18]. The time taken to achieve complete clearance in this study appears to confirm the critical role for dissolution therapy. Unlike Sackmann *et al.*[2], we have added a terpene compound to the bile salt mixture and this may have enhanced dissolution. Terpenes may also have a significant antispasmodic effect, thus reducing the episodes of biliary colic during dissolution therapy[14]. It is of interest to note that only 13 per cent of our patients have suffered with episodes of biliary colic, compared with 35 per cent in the report by Sackmann *et al.*[2].

Overall, our morbidity with lithotripsy and with dissolution therapy has been low. Piezoelectric lithotripsy appears harmless at the doses we have used and is well tolerated by patients without analgesia or sedation[3]. Repeated treatment at these dosages has had no untoward effect, when treatments are separated by intervals of at least 1 week[10]. A few patients, particularly the elderly, experienced back discomfort when lying prone, and this has sometimes had to shorten their treatment time.

It is difficult to assess the exact role for ESWL and dissolution therapy in the future management of patients with gallstones. Patient acceptability is high as the treatments give little or no discomfort. Costs of treatment in our hands would compare favourably with those of cholecystectomy, and the complications are few. However, the late costs, particularly in terms of stone recurrence and their possible complications are, as yet, unknown. The treatment of gallstones is in a state of flux at present with the addition of other newer procedures such as percutaneous intubation and direct gallstone dissolution[19], percutaneous cholecystlithotomy[20,21], and laparoscopic cholecystectomy. The future management of patients with gallstones may incorporate many of these techniques adapted to suit specific situations. Our results would suggest that ESWL and dissolution therapy will have a role in the treatment of a substantial number of patients with gallstones.

In summary, this preliminary report of piezoelectric lithotripsy strongly suggests that the currently accepted criteria for this method of treatment underestimate the number of patients with gallstones that are suitable for this form of therapy. Extended follow-up of our patients is required to determine whether these encouraging early results in terms of gallstone clearance are maintained, and to determine the long-term effects on symptoms.

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Role of fine catheter peritoneal cytology and laparoscopy in the management of acute abdominal pain

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Laparoscopy and fine catheter peritoneal cytology (FCPC) have been advocated as aids in the assessment of acute abdominal pain. In all, 411 patients admitted to a district general hospital during a 10-month period were managed using a standard protocol incorporating these techniques. After initial assessment by a surgical registrar, 151 patients were excluded from further progress through the protocol (age less than 16 years, definite diagnosis made or contraindication to FCPC. The remaining 260 patients were placed in one of four management groups. (A) urgent operation (23 patients); (B) 'look and see' (40 patients); (C) 'wait and see' (59 patients); (D) urgent operation not indicated (138 patients). Eighty-eight of 99 patients (88 per cent) in groups B and C, where the need for operation was uncertain, underwent successful FCPC and 39 patients (39 per cent) underwent laparoscopy. In these patients the initial registrar management decision proved to be incorrect in 33 cases (33 per cent), but by following the protocol the number of management errors actually made was reduced to 13 (13 per cent, $P<0{\cdot}001$). This would have been reduced to 8 per cent if the protocol had not been violated in five patients. This study demonstrates the effectiveness of a protocol using FCPC and laparoscopy to improve the management of patients with acute abdominal pain.

The decision to operate on a patient with acute abdominal pain is usually made by a junior surgeon and when routine investigations have failed to identify its cause, laparotomy is the next option. This is particularly true if the diagnosis is considered to be acute appendicitis when the management error rate (the number of normal appendices removed) has been shown to be as high as 50 per cent and seldom lower than 15 per cent even after consultant assessment[1–4]. Accuracy is highest in young male patients, but is far lower in children and women of child-bearing age[5]

A negative laparotomy may have complications[4,6,7] and removal of a normal appendix is accompanied by immediate and long-term complications in up to 20 per cent of patients[4,5,8]. Conversely, patients with acute inflammatory conditions managed non-operatively until the need for surgery becomes more clinically apparent, may suffer an increased morbidity[1]. Attempts have been made to improve the accuracy of diagnosis of acute abdominal pain but currently there is no available and accepted method[1,5,8 9]

Early results of FCPC in the diagnosis of acute abdominal pain have been encouraging[10–12] and laparoscopy has been shown to be useful in the assessment of such patients[2,6,13–18]. There is evidence that patients managed according to a protocol may do better than those whose treatment is determined by the free choice of a clinician[19] The value of a standard protocol in the management of patients with acute abdominal pain, using both selective FCPC and laparoscopy, was therefore assessed.

Patients and methods

Patient management

Patients presenting with acute abdominal pain to a district general hospital during a 10-month period were managed using a standard protocol (*Figure 1*) Each registrar was free to break the protocol if the management for any individual patient was felt to be unsafe The study was suspended when locum registrars were on duty

After initial assessment by a surgical registrar, patients were assigned to one of five management groups urgent operation indicated (group A), 'look and see' (group B), 'wait and see' (group C), urgent operation not indicated (group D) and exclusion (group E) Patients were placed in group A if they definitely needed an urgent laparotomy except women with acute right iliac fossa pain who were placed in group B Other patients were placed in group B if there was uncertainty but they would normally have proceeded to surgery and in group C when a period of observation would have been recommended If urgent surgery was thought not to be indicated the patient was placed in group D Patients

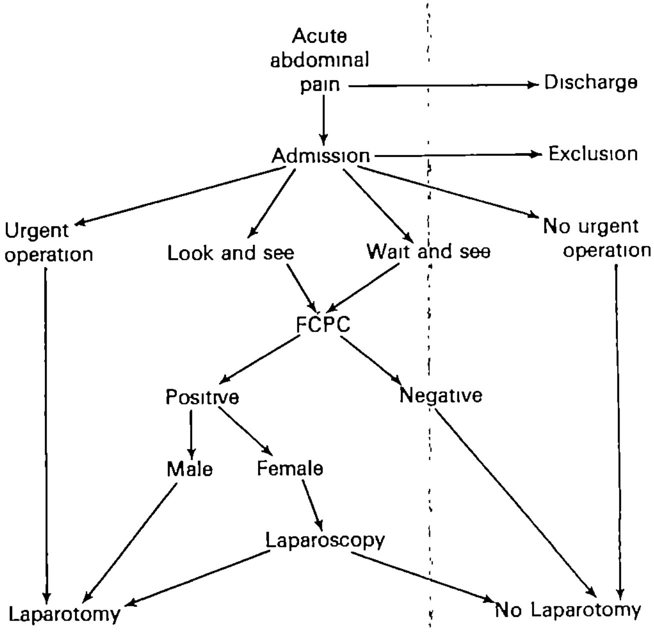

Figure 1 *Protocol for the management of patients with acute abdominal pain FCPC, fine catheter peritoneal cytology*

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were placed in group E and excluded from further progress through the protocol if they were under 16 years of age, if there was a contraindication to FCPC (e.g. previous subumbilical laparotomy incisions or ascites), if a definite diagnosis had been made (e.g. acute pancreatitis, ureteric colic) or they refused FCPC

Patients in groups B and C had FCPC performed. If this was positive (see below) then male patients underwent laparotomy and female patients laparoscopy followed by laparotomy if indicated. If FCPC was negative the patient was managed non-operatively and observed If FCPC was unsuccessful the patient was managed according to the original decision.

The study was approved by the Ealing Hospital Ethical Committee.

Fine Catheter Peritoneal Cytology (FCPC)

FCPC was performed in the accident and emergency department in a standard manner. Consent was obtained and the patient asked to pass urine. Abdominal puncture was performed in the midline immediately below the umbilicus. Sterile precautions were taken and local anaesthetic was infiltrated into the abdominal wall. An intravenous cannula (14 gauge Argyle Medicut, Sherwood Medical, Tullamore, Ireland) was inserted through the abdominal wall and a 3·5 Ch umbilical cather (Argyle, Sherwood Medical, Crawley, UK) was passed through the sheath into the peritoneal cavity. The catheter was manipulated within the abdomen especially in the direction of maximal tenderness, while negative pressure was applied with a 10 ml syringe If the patient were obese a larger cannula (Abbocath, Abbott, Sligo, Ireland) was used.

In a side room the aspirate was deposited onto a glass slide and a thin smear made which was allowed to air-dry. The slide was stained by the Romanowsky method (Hema Guer, BDH Ltd, Poole, UK) Some of the sample was also placed on a patch test strip for granulocytes (Nephur-Test+Leuco, Boeringer Mannheim, GmbH, Mannheim, Germany) and the reaction after 2 min was recorded

The registrar examined the cell profile by microscopy and assessed the peritoneal neutrophil percentage (the percentage of nucleated cells that were neutrophils) and on the basis of previous studies[10,11,20] FCPC was called positive if this count was greater than 50 per cent.

Laparoscopy

After catheter drainage of the bladder, the abdomen was insufflated under general anaesthesia with carbon dioxide and the laparoscope inserted via a subumbilical stab incision The patient was examined in both the Trendelenberg and reverse Trendelenberg positions and a probe, introduced separately, was used to manipulate the organs when necessary

Assessment of patient management

After each patient's discharge the diagnosis and management was analysed. A management error was defined as an unnecessary laparotomy, an unnecessary laparoscopy after a negative or failed FCPC, or an unnecessary delay before appropriate laparotomy. A protocol failure occurred if the patient was retrospectively assessed to have been incorrectly managed (management error) despite the protocol having been followed. A protocol violation occurred when the registrar's management deviated from the protocol described above Data were analysed using the χ^2 test

Results

In all, 411 patients were entered into the protocol. There were 23 patients assigned to group A, 40 to group B, 59 to group C, 138 to group D and 151 to group E The final diagnoses of all patients are shown in *Table 1*. The 151 patients in group E who were excluded from further progress through the protocol included 64 patients aged less than 16 years, seven patients with subumbilical laparotomy scars, three patients with ascites and one patient who refused FCPC.

FCPC

The 99 patients in groups B and C were those patients whom the registrar felt uncertain of the need to operate. FCPC was attempted on all of these patients but was unsuccessful on 11 (11 per cent) because of failure to penetrate the peritoneal cavity (nine patients) or owing to a bloody tap (two patients). There were no complications. FCPC was successful in 88 (89 per cent) patients of whom 39 had a positive and 49 a negative result.

Seven men had a positive FCPC; five had acute appendicitis and two had an inflamed caecal diverticulum which in one patient had perforated. Thirty-two women had a positive FCPC, 29 proceeding to laparoscopy ± laparotomy (see below) while three who had acute appendicitis went straight to laparotomy. The final diagnoses in these women were acute appendicitis (24 patients), pelvic inflammatory disease (five patients), and ectopic pregnancy (three patients).

Forty-nine patients had a negative FCPC. Forty-four patients were observed and 43 did not require surgery, the discharge diagnoses being non-specific abdominal pain (35 patients), urinary tract infection (five patients) and pelvic inflammatory disease (three patients). One man who had been assessed as 'wait and see' (group C) deteriorated and had an inflamed appendix removed the following day. A negative FCPC was ignored by the registrar in the remaining five patients who all underwent unnecessary laparoscopy and/or laparotomy.

FCPC failed in 11 patients (11 per cent). Three patients (one woman, two men) who had been placed in group C were observed. Symptoms in all three resolved without surgery. The other eight patients, who were all female, had been placed in group B Two did not have laparoscopy attempted because they were considered too obese but underwent surgery which yielded acute appendicitis in one and a normal appendix in the other. Six women had laparoscopy ± laparotomy (see below) with final diagnoses of non-specific abdominal pain (four patients), acute appendicitis (one patient) and urinary tract infection (one patient).

The granulocyte patch test strip reaction did not correlate well with the FCPC result. In 31 patients with acute appendicitis whose FCPC results were positive, the patch test was positive

Table 1 *Final diagnoses in all patients according to group*

Diagnosis	Group A ($n=23$)	Group B ($n=40$)	Group C ($n=59$)	Group D ($n=138$)	Group E ($n=151$)
Appendicitis	21	20	12		16
Mesenteric adenitis			1		9
Non-specific abdominal pain		8	36	44	39
Gallstones				28	2
Pancreatitis					13
Intestinal obstruction					22
Urinary tract infection		1	5	15	
Pelvic inflammatory disease		5	1		
Renal colic					30
Malignancy				16	1
Diverticular disease				10	
Other	2	6	4	25	19

(>75 granulocytes per μl) in only 23 (74 per cent) patients. In 39 patients with non-specific abdominal pain whose FCPC results were negative, the patch test was negative (<75 granulocytes per μl) in only 34 (87 per cent). Moreover, if the aspirate was contaminated with blood the patch test colour change was difficult to interpret. Occasionally there was insufficient peritoneal aspirate to prepare both a slide and a patch test strip.

The time required for FCPC and microscopy was approximately 20 min.

Laparoscopy

The surgeons involved in this study had varied experience of laparoscopy, and the results detailed below include the early experience of some surgeons. None the less all surgeons soon became confident in this technique.

Of the 32 women with a positive FCPC, 29 underwent laparoscopy which was successful in 28 but failed in one obese patient who underwent immediate laparotomy for acute appendicitis. Five laparoscopies revealed pelvic inflammatory disease and these women did not proceed to laparotomy. The other 23 women underwent laparotomy on the basis of their laparoscopic findings; 20 had acute appendicitis, two had ectopic pregnancies, and one had a normal appendix removed because the appendix was not visible at laparoscopy and the pelvic organs appeared normal. Two weeks later this patient was readmitted with recurrent pain, and repeat laparoscopy showed an ectopic pregnancy.

Six women underwent laparoscopy after failed FCPC. This was unsuccessful in two obese patients in whom subsequent laparotomy showed a normal appendix in each case. One laparoscopy showed an acutely inflamed appendix which was removed. The remaining three laparoscopies were normal and a urinary tract infection was later diagnosed in one patient.

Laparoscopy was performed in four patients with a negative FCPC where the registrar chose to break the protocol. In two patients no abnormality was seen and laparotomy was therefore avoided. In the other two patients the appendix was not visualized and subsequent laparotomy showed non-inflamed appendices.

Laparoscopy was attempted on 39 patients, was successfully performed in 36 (92 per cent) patients and an unnecessary laparotomy was prevented in ten patients originally placed in group B ('look and see'). In 23 patients appropriate laparotomy was performed on the basis of laparoscopic findings. Three patients had an unnecessary laparotomy after laparoscopy.

Assessment of patient management

There were eight protocol violations. The registrar ignored a negative FCPC in five patients and three women who had positive FCPC results did not have laparoscopy before laparotomy for acute appendicitis. Six of the eight protocol violations occurred during the first 3 months of the study, one occurred in the fifth month and the last in the tenth month.

There were no management errors in patients in groups A or D, but seven occurred in group E where normal appendices were removed from six children and one women who refused FCPC. The unnecessary appendicectomy rate in group E was therefore 30 per cent (seven of 23 patients).

In groups B and C there were 13 management errors. Five occurred when the registrar ignored a negative FCPC and proceeded to unnecessary laparoscopy and/or laparotomy. Six occurred in patients in group B on whom FCPC failed, although laparoscopy prevented unnecessary laparotomy in three of them. In two of these patients FCPC was repeated under general anaesthesia and found to be negative. One patient had an ectopic pregnancy missed at laparoscopy and a subsequent negative appendicectomy. One patient had a delayed appendicectomy for acute appendicitis because FCPC was falsely negative (peritoneal neutrophil percentage = 5 per cent). This last management error represents the only protocol failure.

The overall management error rate for all groups was 4·9 per cent. In groups B and C the initial registrar management decision was shown to have been incorrect in 33 (33 per cent) cases, but by following the protocol, the number of management errors actually made was reduced to 13 (13 per cent) ($P<0·001$). Six of the 13 errors occurred when FCPC failed. A further five errors occurred when the registrar broke the protocol. Thus the management error rate in these two groups would have been reduced to 8 per cent if there had been no protocol violation.

Discussion

This study is the first to use a combination of FCPC and laparoscopy in a defined management protocol for patients with acute abdominal pain. The protocol has proved easy to apply and it has resulted in a significant reduction in the management error rate. There was only one protocol failure

A recent review of diagnostic aids in the management of acute appendicitis concluded that barium enema, ultrasound scanning, laparoscopy and computer aided diagnosis were the most valuable[1]. Apart from laparoscopy, however, these aids are frequently not available for urgent patient assessment[21]. Laparoscopy has been shown to be extremely accurate in the diagnosis of acute abdominal pain and the incidence of complications is lower than that of negative laparotomy[2,12–15] but it is invasive and requires general anaesthesia.

When making management decisions, FCPC is attractive because it is simple and safe to perform and requires no special equipment. These results confirm that FCPC reliably detects the presence of acute intraperitoneal inflammation and when positive in a man almost always indicates the need for laparotomy. There is a wider differential diagnosis for intraperitoneal inflammation in women with acute abdominal pain, and laparoscopy is useful to identify inflammatory conditions not requiring laparotomy. FCPC plays an important role in minimizing the number of unnecessary laparoscopies performed.

When FCPC failed, laparoscopy prevented several unnecessary laparotomies. As in previous studies the appendix was sometimes not directly visualized[2,6,11,13–15,17] but indirect signs of inflammation were evident so that appendicitis was never missed.

The potential management error rates in the 'uncertain' groups and the actual unnecessary appendicectomy rate in the exclusion group (almost all children) was comparable at about 30 per cent. Patients managed according to a protocol may do better than those whose treatment is determined by the free choice of a clinician although the protocol regimen may have no more effective treatment options than those available to the clinician[18,19]. Possible reasons for this include greater commitment by those involved in the protocol, the training effect of the protocol and the avoidance of detrimental management shortcuts. While this hypothesis is by no means proven it may have been significant in this and similar studies. Included in any protocol must be the right of the clinician to break the protocol, and in this study protocol violation occurred less frequently with time, presumably as the registrars involved realized its reliability.

Some of the studies reporting the lowest unnecessary laparotomy rates have followed a policy of 'active observation'[22]. Frequent re-examination of patients under observation with acute abdominal pain is an alternative to the management protocol used here. A policy of 'active observation' is frequently difficult to implement for busy and stressed junior surgeons[23] The protocol described reduces the uncertainty and anxiety involved in the management of patients with acute abdominal pain.

We conclude that FCPC and laparoscopy can play a valuable role in improving the management of patients with acute abdominal pain expecially in the form of the protocol described in this paper.

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Population-based study of surgery in juvenile onset Crohn's disease

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A geographically based cohort of 68 children with Crohn's disease was derived by sampling from Scottish Hospital In-patient Statistics. Surgical histories were examined and analysed by actuarial methods, and the nature of major operations performed was compared with operations for Crohn's disease in the Lothians' Surgical Audit. Fifty-four of the 68 patients were treated surgically, with a total of 135 operations (71 major, 64 minor). Fifty per cent of the cohort had a major operation within 5 years of onset of symptoms; median time to a second operation was 4 years. The types of major operation performed in juvenile onset patients differed significantly from those recorded in the Lothians' audit, with a high rate of exploratory laparotomy in younger patients (12 cases). With a mean follow-up of 7 years, 12 patients (18 per cent) have a permanent stoma. There were five deaths, three postoperative. This study highlights the frequency of surgical intervention in young people with Crohn's disease.

Analysis of Scottish Hospital In-patient Statistics (SHIPS) for 1968–83 has revealed a threefold rise in the incidence of juvenile onset Crohn's disease and a marginal fall in ulcerative colitis incidence during these 15 years[1]. In parallel with the epidemiological study, the SHIPS database was also used to derive a large, population-based sample of patients with juvenile onset inflammatory bowel disease for documentation of clinical features, natural history and prognosis. Review of the case records of these 105 patients has revealed substantial morbidity, particularly in Crohn's disease, including a high operation rate[2].

We have examined in detail the operative data for the cohort with Crohn's disease in order to define the types of operation performed and to determine whether these differ from operations for Crohn's disease in adults. Life table analysis has been used to establish the likelihood, in an individual patient, of having one or two major operations. The data have also allowed us to examine the influence of site of disease at presentation on subsequent operative intervention, and on the risk of requiring a permanent stoma.

Patients and methods

Identification of a cohort of patients with juvenile onset Crohn's disease

In Scotland, the Common Services Agency maintains central records of all hospital in-patients, and record linkage is used to combine multiple admissions of the same patient[3,4]. From the SHIPS database 1968–83, a list of all patients aged under 20 years admitted to a National Health Service hospital in Scotland with the diagnosis coded as Crohn's disease was obtained As fully described elsewhere[1,2], and with permission from the consultant in charge, case records from all patients on the list resident in the Lothian and Highland regions and of a random 10 per cent sample of patients resident in the other nine regions were reviewed The final study cohort comprised 68 patients in whom the onset of symptoms attributable to Crohn's disease began before or at 16 years of age, who satisfied standard diagnostic criteria[5], and whose case records were available for review Details of surgical procedures were abstracted from the notes.

Operations in adult patients with Crohn's disease

In Edinburgh and the Lothians, details of operations performed and surgical mortality have been recorded prospectively since 1946 These audit statistics do not include data from paediatric surgical units. Procedures are coded by the surgeon detailing the organ involved, the disease process and the nature of the operation[6]. Operative data from 1983 to 1987, where the disease code was Crohn's disease, were analysed for comparison with the data for juvenile onset disease.

Nature and classification of operations performed

Major and minor operations Any procedure in which the peritoneum or urinary tract was opened was classified as major Minor operations comprised all other procedures carried out under general anaesthesia Unrelated operations, for example those for trauma, were excluded.

Combined procedures. In instances where more than one procedure was performed during an operation, the more major procedure has been used to classify the types of operation performed.

Nomenclature The term 'laparotomy' is used to include inspection of the peritoneal cavity with or without biopsy or appendicectomy, and with no resection or bypass performed. 'Small bowel resection' includes jejunal resection, ileal resection and terminal small bowel resection with amputation of the caecum.

Statistics

The types of operation performed in juvenile onset and adult Crohn's disease were compared by χ^2 analysis. Life table analysis was performed by the method of Hill[7] and the log rank test used to compare the curves drawn from the life tables[8].

Results

Patients studied

The study group comprised 68 patients, 34 male 34 female. The mean(s.d.) age at onset was 12·5(3·49) years with a range of 2·25–16·9 years. At presentation, 17 had disease confined to the small intestine, 16 to the colon, 30 had both small and large bowel affected and five had either oral or perianal disease. Duration of follow-up ranged from 1·25 to 18·7 years with a mean(s.d.) of 7·05(4·2) years. A more detailed description of symptoms and other clinical features has been published elsewhere[2]

Operations performed in patients with juvenile onset Crohn's disease

In all, 135 operations (71 major, 64 minor) were performed in 54 of the 68 patients. Forty-one patients had one or more major operation; mean(s.d.) age at first major operation was 16·5(3·7) years and mean(s.d.) age at second major operation was 18·8(3·8) years. The operation rate was the same for both sexes. The types of operation are detailed in *Table 1*. Of particular interest is the relatively high number of laparotomies (12) and the low rate of bypass surgery, these comprising one ileotransverse bypass, a gastroenterostomy and a defunctioning

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ileostomy. Strictureplasty is not included in *Table 1*; this was performed in one patient in combination with a small bowel resection. Twelve of the 71 major operations were combined procedures (*Table 2*). *Figure 1* summarizes the nature of second and subsequent operations, analysed in relation to the type of operation performed on the first occasion.

Of the 64 minor procedures undertaken under general anaesthetic, 27 were for simple examination under anaesthesia with or without endoscopy, and a further 27 involved perianal surgery.

Table 1 *Types and numbers of operations for Crohn's disease*

Operation	Juvenile onset	Lothian adult surgical units
Major		
Laparotomy	12*	9
Small bowel resection	20	161
Small bowel bypass/diversion	3	10
Segmental colonic resection with restoration	17	93
Total colectomy/panproctocolectomy	10	44
Abdominoperineal	0	23
Colostomy alone	3	7
Others	6†	39‡
Total	71	386
Minor		
EUA/endoscopy	27	113
Anal and perianal procedures	27	79
Others	10	124
Total	64	316
All operations	135	702

EUA, examination under anaesthetic. * Includes four with appendicectomy, † two divisions of postoperative adhesions, one pyelolithotomy, three closures of stoma, ‡24 stoma revisions and closures, six Hartmann's resections, five divisions of adhesions, four proctectomies

Comparison of operations in juvenile onset Crohn's disease with operations in Lothian adult surgical units

Of the 131 896 operations performed in Lothian between 1983 and 1987, 578 (0·44 per cent) were for Crohn's disease, 386 major, 316 minor. The ratio of major to minor procedures was similar in juveniles ($P<0{\cdot}025$).

The types of operation performed in adult surgical units are listed in *Table 1*. Comparison of major operations performed in juvenile onset and adult patients revealed a significant difference ($\chi^2=37{\cdot}130$; d.f. $=7$; $P<0{\cdot}001$). This was due to the higher laparotomy rate in the juveniles (17 per cent) compared with adults (2 per cent), a larger proportion of small bowel resections in adults, and the absence of abdominoperineal resection in juveniles.

Life table analyses of major operations in patients with juvenile onset Crohn's disease

Figure 2 shows an actuarial analysis of the risk of having a first or second major operation in the cohort. Within 5 years of onset of disease, 50 per cent had a first major operation and 94 per cent

Table 2 *Juvenile onset Crohn's disease combined procedures*

Major procedure	Additional procedure
Laparotomy	Excision of Meckel's diverticulum Colonoscopy
Small bowel resection	Excision of right fallopian tube Anterior resection and transverse colostomy Ureterolysis Appendicectomy Excision of ileocolic fistula Drainage of iliopsoas abscess Anterior resection Gastroenterostomy Stricturoplasty Ileostomy, defunctioning colostomy and incision and drainage of pelvic abscess

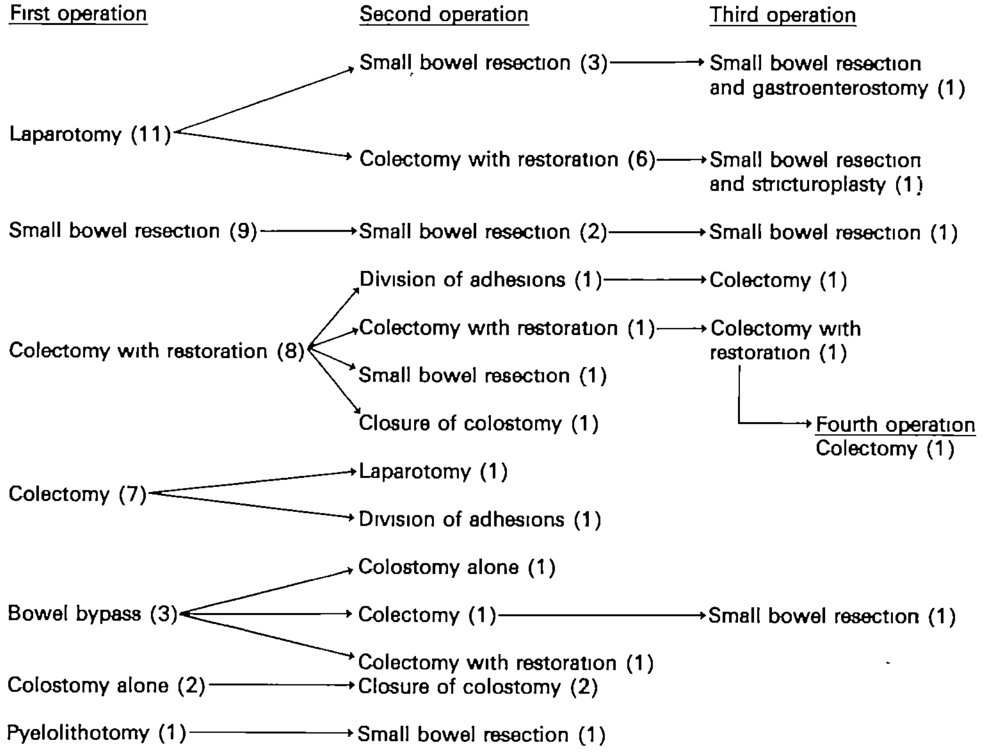
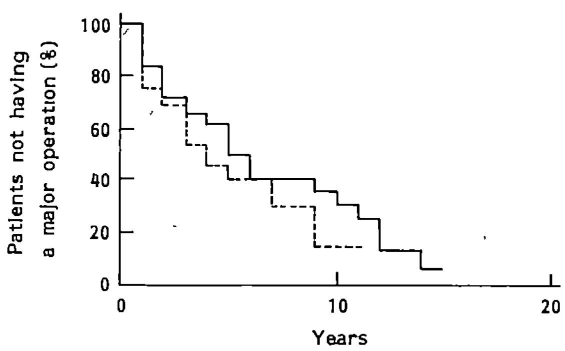

First operation
Second operation
Third operation
Laparotomy (11)
Small bowel resection (3)
Small bowel resection and gastroenterostomy (1)
Colectomy with restoration (6)
Small bowel resection and stricturoplasty (1)
Small bowel resection (9)
Small bowel resection (2)
Small bowel resection (1)
Colectomy with restoration (8)
Division of adhesions (1)
Colectomy (1)
Colectomy with restoration (1)
Colectomy with restoration (1)
Small bowel resection (1)
Closure of colostomy (1)
Fourth operation
Colectomy (1)
Colectomy (7)
Laparotomy (1)
Division of adhesions (1)
Bowel bypass (3)
Colostomy alone (1)
Colectomy (1)
Small bowel resection (1)
Colectomy with restoration (1)
Colostomy alone (2)
Closure of colostomy (2)
Pyelolithotomy (1)
Small bowel resection (1)

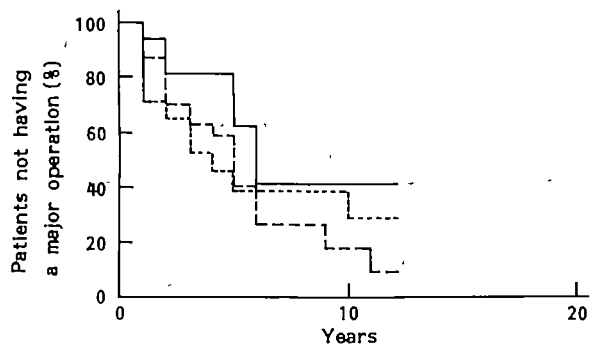
Figure 1 *Nature of second and subsequent operations in patients with Crohn's disease, analysed according to the type of operation performed on the first occasion*



First operation																
Years since onset	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Not had 1st operation	68	57	46	40	34	22	14	9	9	8	6	4	2	2	1	1

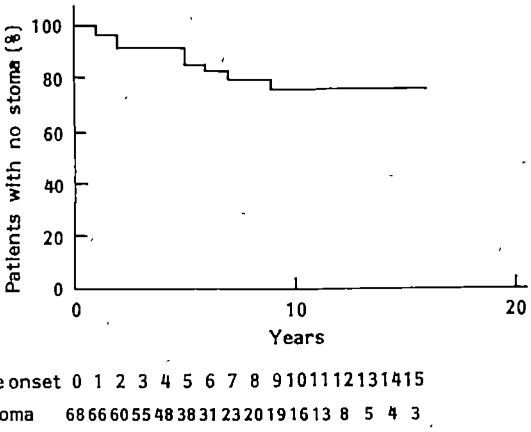
Second operation													
Years since 1st operation	0	1	2	3	4	5	6	7	8	9	10	11	12
Not had 2nd operation	41	24	18	14	10	8	8	5	4	2	2	2	0

Figure 2 *Actuarial analysis of the timing of the first (——) or second (---) major operation in the cohort of 68 patients with juvenile onset Crohn's disease. The curves for first and second major operations are not statistically different*



Years since onset		0	1	2	3	4	5	6	7	8	9	10	11	12	13
Not had 1st operation	---	17	12	11	8	7	5	4	4	4	4	2	2	0	2
	-----	30	26	19	17	15	7	3	3	3	2	2	1	1	1
	——	16	15	12	12	9	6	4	1	1	1	1	1	1	1

Figure 3 *Actuarial analysis of the timing of the first major operation in juvenile onset Crohn's disease, subdivided according to site of disease at the time of diagnosis ---, small and large bowel; ——, small bowel only, ——, large bowel only. The curves are not statistically different*



Years since onset	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Not had stoma formed	68	66	60	55	48	38	31	23	20	19	16	13	8	5	4	3

Figure 4 *Actuarial analysis of the timing of the creation of a permanent stoma in juvenile onset Crohn's disease*

of those at risk had major surgery within 15 years. Of the 41 patients who had undergone a first major operation, 60 per cent had a further major operation within 5 years, 85 per cent within 10 years. The curves for first and second major operation are not statistically different. Numbers are too small at present for analysis of third and subsequent operations.

Figure 3 shows life table analyses of the first major operation, subdivided according to site of disease at the time of diagnosis. Thirty patients had ileocolic disease, 16 large bowel only and 17 small bowel only. Within 5 years of onset, 19 per cent of those with large bowel disease, 54 per cent with small bowel disease alone and 42 per cent with both large and small bowel disease had an operation, rising to 59 per cent, 61 per cent and 82 per cent at 9 years. These raw data suggest that colonic disease may be less aggressive and require less surgery

Stomas in juvenile onset Crohn's disease

Fifteen patients had a stoma fashioned. In three this was a temporary colostomy; one patient had a permanent colostomy, ten had a permanent ileostomy and one patient had both ileostomy, and colostomy fashioned at the same time (this patient died 30 days after surgery). Mean(s.d.) age at which a permanent stoma was fashioned was 18(4·4) years, range 10·7–24 years. Life table analysis shows that 14 per cent of patients have a permanent stoma within 5 years of onset of disease, rising to 24 per cent within 10 years (*Figure 4*).

Deaths of patients with juvenile onset Crohn's disease

Deaths of patients in this series have been detailed in an earlier paper[2] and the relevant information is summarized in *Table 3* Three of the five deaths were postoperative, occurring at 7, 14 and 30 days after surgery.

Discussion

The rising incidence of inflammatory bowel disease in young people is due entirely to a change in the number with Crohn's disease, which is now commoner than ulcerative colitis in this age group In Scotland in 1983, the recorded incidence of Crohn's disease in children aged 0–16 years was 22·9 per million, and of ulcerative colitis 15·6 per million (age range 6–16 years)[1]

Retrospective review of the surgical histories of our population-based cohort has revealed a high operation rate, with 54 of 68 patients undergoing 135 procedures, the mean duration of follow-up being just over 7 years. The relevant literature shows wide variation in crude operation rate, which can be explained by heterogeneity of case mix, definitions of operation, wide age ranges of patients (up to age 20 or 21 years in some series) and study periods ranging from 1935 to 1983 (*Table 4*). Two studies are reasonably comparable to ours. Krebs and Nixon[14] from Great Ormond Street reported 39 children, prepubertal and pubertal at onset of disease, of whom 24 had 36 major operations. Puntis *et al.*[9] reported 89 resections in 54 of 67 children admitted to the Birmingham Children's or General Hospitals. Both series are from referral centres, and neither describes minor or non-definitive procedures.

Actuarial analysis of our data shows that 50 per cent of patients with Crohn's disease had a major operation within 5 years and 94 per cent by 15 years after onset These figures are almost the same as those from Great Ormond Street, 44 per cent within 5 years and 93 per cent within 14 years. In our series, of those patients who had already had one operation, 59 per cent had a second within a further 5 years.

It seemed possible that, for reasons related both to patterns of disease and clinical philosophy, surgical practice in juvenile onset Crohn's disease might differ from that in adults with inflammatory bowel disease. We therefore compared our results with the Lothian Surgical Audit figures which describe only the number and type of operations without patient record linkage and include operations performed on patients referred from other National Health Service regions and also some

Table 3 *Summary of deaths of patients with juvenile onset Crohn's disease*

Sex	Age at onset (years)	Disease extent	Surgery (age in years)	Mode of death	Age/year at death
M	14	S, L, F	1. Right hemicolectomy (16·25) 2. Small bowel resection (24·9)	Bowel obstruction, bacteraemia	25 1/1978
M	14	S, L, F, A	1. Excision fistula-in-ano (15·5) 2. Small bowel resection, ileostomy, colostomy, pelvic abscess drained (19·5)	Peritonitis, bacteraemia	19 6/1972*†
F	9	S, L	1. Laparotomy and ileostomy (10·7) 2. Panproctocolectomy (16·9) 3. Laparotomy (19·6)	Peritonitis, bacteraemia	19 6/1974*
F	10	L	None	Depression, anorexia, malnutrition	14 4/1974
F	10	L, F, A	1. Panproctocolectomy (11·65)	Abscess, bacteraemia	11 7/1973*

S, small bowel; L, large bowel; A, anal; F, fistula, * postoperative death; † 30 days postoperative

Table 4 *Published series of operations for juvenile onset Crohn's disease*

Study	Years reviewed	Total no of patients	Age range at onset (years)	Mean follow-up (years)	Patients having operations (%)	No. of operations	Comments
Puntis[9]	1935–80	67	3–16	16·5	57 (85)	89	Only resections recorded as operations 12 per cent permanent stoma
Guttman[10]	1949–73	52	<19	6·9	28 (54)	33	60 per cent patients of Jewish origin Excludes laparotomies and appendicectomies. No permanent stoma
Castile[11]	1950–73	177	<16	8·8	119 (67)	178	146 non-definitive operations were performed in addition to the 178 definitive. The numbers of operations in the text and tables do not add up. Cumulative reoperation rates calculated. 19 per cent permanent stoma
Ritchie[12]	1950–83	45	<17	9·8	31 (69)	36	Procedures for anal and perianal conditions not recorded 29 per cent permanent stoma
Farmer[13]	1955–74	522	<21	7·7	360 (69)	n.s.	60 per cent of cases age 16–20 Telephone interviews 20 per cent
Krebs[14]	1955–79	39	Before puberty	4·8	24 (62)	36	Cumulative operation rates calculated. 12 per cent permanent stoma
Gryboski[15]	1966–76	86	<20	6	34 (40)	75	Operations comprise 44 major and 31 minor, but exclude three laparotomies. 6 per cent permanent stoma
Bensoussan[16]	1967–79	93	7–19	n.s	39 (42)	52	Cumulative recurrence rates calculated. 4 per cent permanent stoma
Raine[17]	1970–79	80	1–14	4·3	46 (57)	n s.	Patients from 17 British paediatric surgical units. Crude reoperation rate 17 per cent at 1 year
Boeckman[18]	1971–80	41	Up to 10	n s	26 (43)	40	Crude reoperation rate 33 per cent. 24 per cent permanent stoma
Chong[19]	1973–81	54	<18	n.s.	12 (22)	12	No reoperation at 2-year follow-up
Postuma[20]	1974–83	33	<17	2·8	13 (39)	30	Operation no includes laparotomies and procedures for anal/perianal disease. 12 per cent permanent stomas
Present series	1968–83	68	<17	7	54 (79)	135	Operation no comprises 71 major and 64 minor procedures. 18 per cent permanent stomas

n.s., Not specified; all studies other than present series contain cases referred to specialist units

diagnostic flexible endoscopy. The audit figures cover the time period 1983–87, whereas the operations in juveniles were carried out in the 1970s and early 1980s. However, the differences which emerged between the types of operation performed in patients with juvenile onset and adult Crohn's disease are so striking that it is most unlikely that they are due merely to the different sources of information

In the young patients there were more diagnostic laparotomies, relatively fewer small bowel resections and no abdominoperineal resections. The high laparotomy rate

(17 per cent of all major operations) compares with 2 per cent in Lothian adults, but is similar to published series for juvenile onset Crohn's disease[14,16]. In our series nine of the 11 having laparotomy as a first operation subsequently went on to have further surgery with resection.

Examination under anaesthetic is essential for the proper assessment of painful or complex anal, perianal and rectal disease. Anaesthesia may also be necessary for thorough appraisal of the rectal mucosa in a newly presenting, anxious or very young child with proctitis. However, we question the policy of using general anaesthesia for relatively routine follow-up sigmoidoscopies.

The patterns of second and subsequent operations show interesting differences between small bowel and large bowel Crohn's disease after treatment by resection of the affected segment (*Figure 1*). Several patients submitted to small bowel resection with restoration have had further small bowel resections but none has yet had a colonic resection. In contrast, none of the seven patients whose first operation was colectomy with ileostomy has required further surgery for recurrent disease. In many respects these patients resemble those with ulcerative colitis in that (so far) they are apparently cured by colectomy.

The creation of a permanent stoma is a major physical and psychological event for any patient. In this series, the crude rate for patients with Crohn's disease was 18 per cent. Actuarial calculations show that within 5 years of onset 14 per cent have a permanent stoma and by 10 years this has risen to 24 per cent. Crude stoma rates in other series are documented in *Table 4*

When a diagnosis of chronic and essentially incurable disease is made, the patient, relatives and medical practitioners seek information on prognosis, morbidity and mortality. In inflammatory bowel disease questions relating to the need for surgery, and particularly of having a stoma, are often posed. Our data provide answers, based on clinical practice in Scotland in the 1970s and early 1980s. In juvenile onset Crohn's disease the likelihood of having a major operation is 50 per cent at 5 years and 94 per cent at 15 years after onset of symptoms. The likelihood of a second operation is also high – half of those having one operation will have a second within 5 years. With a mean follow-up of 7 years, nearly 20 per cent of the series have a permanent stoma and there is a significant mortality with five deaths, three of which were postoperative.

Acknowledgements

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Population-based study of surgery in juvenile onset ulcerative colitis

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A geographically based cohort of 37 children with ulcerative colitis has been derived by sampling from Scottish Hospital In-patient Statistics. Surgical histories were examined and analysed by actuarial methods, and the major operations performed were compared with operations for ulcerative colitis in the Lothians' Surgical Audit. Fourteen of the 37 patients had a total of 26 operations (15 major, 11 minor). Sixteen per cent had major surgery within 5 years of onset of symptoms, and the types of operation were similar to those recorded in Lothians' Surgical Audit. Operation rate was significantly lower than that for a parallel cohort of patients with Crohn's disease. With a mean follow-up of 7·4 years, seven (19 per cent) patients have a permanent stoma and there has been one death.

A population-based sample of 105 patients with juvenile onset inflammatory bowel disease has been derived by using the Scottish Hospitals In-patient Statistics (SHIPS) data base[1]. Review of the case records revealed substantial morbidity as reflected by symptoms, hospital admissions, operation rate, growth retardation, delayed sexual development and mortality[2]. In all of these aspects, Crohn's disease was associated with a higher morbidity than ulcerative colitis. This short report concerns the number and nature of operations on 37 patients with ulcerative colitis.

Methods

Identification of a cohort of patients with juvenile onset ulcerative colitis

In Scotland the Common Services Agency maintains central records of all hospital in-patients, SHIPS The derivation of a geographically based sample of 37 patients with ulcerative colitis is described elsewhere[2] These were patients in whom the onset of symptoms attributable to inflammatory bowel disease began before or at 16 years of age, who satisfied standard diagnostic criteria for ulcerative colitis[3] and whose case records were available for review. Details of surgical procedures were abstracted from the notes

Operations in adult patients with ulcerative colitis

In Lothians' Surgical Audit, operative procedures are coded by the surgeon who details the organ involved, the disease process, and the nature of the operation[4] Operative data from 1983 to 1987, where the disease code was ulcerative colitis, were analysed for comparison with the data for juvenile onset disease

Nature and classification of operations performed

Any procedure in which the peritoneum or urinary tract was opened was classified as major. Minor operations comprised all other procedures done under general anaesthesia. Operations unrelated to inflammatory bowel disease were excluded.

Statistics

The χ^2 analysis was used for comparing the types of operation in juvenile onset disease and disease in adults. Life table analysis was performed by the method of Hill[5] and the log rank test was used to compare the curves drawn from the life tables[6]

Results

Patients studied

The study group comprised 37 patients, 2 males and 15 females. The mean(s.d.) age at onset was 11·9(4·1) years with a range of 0·25 to 16·8 years. At presentation, 17 patients had extensive colitis, in ten the disease was confined to the distal colon and ten had only rectal disease. Duration of follow-up ranged from 3 months to 18·5 years with a mean(s.d.) of 7·4(4·6) years.

Operations performed in patients with juvenile onset ulcerative colitis

Twenty-six operations (15 major, 11 minor) had been performed in 14 of the 37 patients. Nine patients had at least one major operation, mean(s.d.) age at first major operation was 18·8(7·3) years and the operation rate was the same for both sexes. The types of operation are detailed in *Table 1*. Seven patients had colectomy with ileostomy, including three who had panproctocolectomy and four who had total colectomy with retention of the rectum. In three of the latter, proctectomy was performed 8 months, 6·1 years and 9·2 years later. One patient has had proctocolectomy with creation of an ileal pouch.

The 11 minor procedures included nine rigid sigmoidoscopies under general anaesthesia.

Comparison of operations in juvenile onset ulcerative colitis with operations in Lothian adult surgical units

In the 5-year period 1983–87, 285 operations were performed in the Lothians for adult ulcerative colitis (184 major, 101 minor). In general, major operations in the juvenile onset group were similar to those in adults (*Table 1*).

Life table analysis of major operations in juvenile onset ulcerative colitis

Figure 1 shows an actuarial analysis of the risk of having a first major operation for the cohort of 37 patients. Within 5 years of onset of disease, 15 per cent had a major operation and within 10 years, 26 per cent. Numbers of patients who had a second major operation are too small at present for analysis

Comparison of the likelihood of major surgery in juvenile onset Crohn's disease and ulcerative colitis

The log rank test was used to compare the probability of having a first major operation in Crohn's disease[7] and ulcerative colitis (*Figure 1*). There was a highly significant difference ($t_0 = 12{\cdot}943$; 1 d.f.; $P < 0{\cdot}0005$). A patient with Crohn's disease was three times more likely to have major surgery within 5 years of the onset of symptoms than was a patient with ulcerative colitis.

Stomas in juvenile onset ulcerative colitis

Eight patients had a stoma fashioned at some stage; one temporary and seven permanent ileostomies. Mean(s.d.) age at which a permanent stoma was created was 19·7(7 2) years, range

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10·6–30·8 years Life table analysis shows that 12 per cent of patients have a permanent stoma within 5 years of presentation and 22 per cent within 10 years (*Figure 2*). There was no difference in the permanent stoma rate between juvenile onset Crohn's disease[7] and ulcerative colitis

Deaths of patients with juvenile onset inflammatory bowel disease

Only one patient has died, in the early part of the study period (1970). He had a colectomy at 10·6 years of age and had proctectomy combined with ureterolithotomy 8 months later. At 12·3 years of age he presented with small bowel obstruction, perforation and septicaemia and died before coming to further surgery.

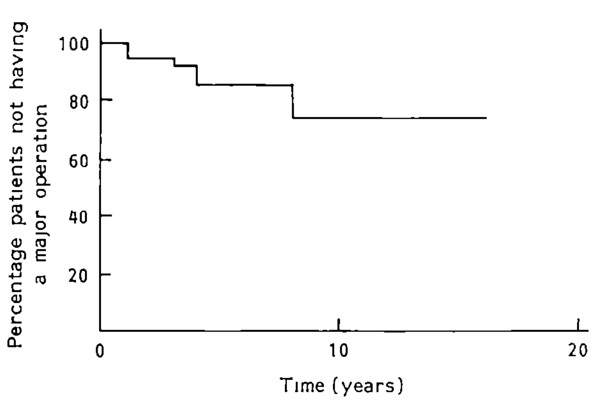
Discussion

Relatively little has been written on the surgery of juvenile onset ulcerative colitis (*Table 2*). In the limited literature the age range and duration of follow-up vary considerably, there are no data from geographically based cohorts, and only one study employed

Table 1 *Types and numbers of operations for ulcerative colitis*

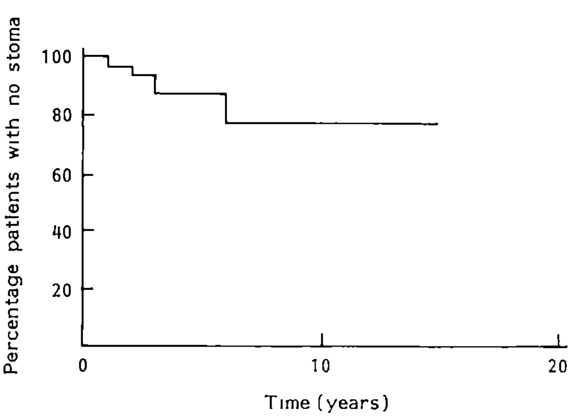
Operations	Juvenile onset	Lothian adult surgical units
Major		
Laparotomy	1	2
Segmental colonic resection with restoration	0	18
Colectomy and ileostomy	7	108
Colectomy and ileorectal anastomosis	0	6
Proctocolectomy and pouch	1	1
A-P Hartmann's resection	0	5
Proctectomy	3	6
Colostomy alone	0	5
Others	3*	33†
Total	15	184
Minor		
EUA/endoscopy	9	95
Others	2	6
Total	11	101
All operations	26	285

A-P, abdominoperineal, EUA, examination under anaesthetic *One division of postoperative adhesions, one stoma revision, one closure of stoma †Ten reanastomoses, two enterocolic bypasses, 15 stoma revisions and closures



Years since onset	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Not had first operation at start of year	37	32	31	25	24	19	17	12	12	10	8	8	4	4	4	2

Figure 1 *Actuarial analysis of the timing of the first major operation in juvenile onset ulcerative colitis*



Years since onset	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Not had stoma formed	37	33	32	26	25	20	16	13	13	10	8	8	4	4	4	2

Figure 2 *Actuarial analysis of the timing of the creation of a permanent stoma in juvenile onset ulcerative colitis*

Table 2 *Published series of operations for juvenile onset ulcerative colitis*

Study	Years reviewed	Total no. of patients	Age range at onset (years)	Mean follow-up (years)	Patients having operations	No. of operations	Comments
*Ehrenpreis[8]	1953–65	225	<17	NS	45 (20)	NS	14 per cent permanent stoma
*Michener *et al*[9]	1955–74	336	<21	11·8	119 (35)	NS	13 per cent permanent stoma
*Foglia *et al.*[10]	1956–76	47	<19	NS	47 (100)	79	Surgical series, 100 per cent permanent stoma
*Krebs and Nixon[11]	1955–79	102	Before puberty	5 9	30 (29)	41	Cumulative operation rates calculated, 50 per cent permanent stoma
*Telander *et al*[12]	1960–79	100	<19	6 9	100 (100)	135	Surgical series, 55 per cent permanent stoma
*Raine[13]	1970–79	73	1–14	5·1	19 (26)	NS	Patients from 17 UK paediatric surgical units, 15 per cent permanent stoma
*Chong and Walker-Smith[14]	1973–81	17	<17	NS	3 (18)	NS	
Present series	1968–83	37	<17	7 0	14 (38)	26	Operation number comprises 15 major and 11 minor procedures, 19 per cent permanent stoma

Values in parentheses are percentages. * Referred cases to specialist units, NS, not specified actuarial methods to calculate operation rates[8]. We found the operation rate in ulcerative colitis to be considerably lower than in Crohn's disease. By 5 years after onset only 15 per cent of patients had had a major operation, rising to 26 per cent at 10 years. The Great Ormond Street series[11] gave similar results, with 22 per cent at 5 years after onset and 44 per cent at 10 years This contrasts with the figure of 50 per cent of patients with Crohn's disease who have had major surgery within 5 years of presentation.

The major operations performed in the juvenile onset ulcerative colitis cohort do not differ significantly from those in Lothians' Surgical Audit, and as the study runs only up to the mid-1980s, it was not surprising to find only one sphincter-saving operation. Colectomy with ileorectal anastomosis, proctocolectomy with ileoanal anastomosis and panproctocolectomy with continent ileostomy were not performed.

Crude stoma rate was 19 per cent and actuarial calculations show that within 5 years of onset 12 per cent of patients have a permanent stoma with 22 per cent by 10 years; these are similar to the stoma rates for juvenile onset Crohn's disease[7]. Crude stoma rates in other series are given in *Table 2*; there are no published reports of stoma rates calculated by actuarial methods in juvenile onset inflammatory bowel disease.

These data, based on clinical practice in Scotland in the 1970s and early 1980s, show that surgical intervention in juvenile onset ulcerative colitis is much less frequent than in Crohn's disease; the likelihood of having a major operation is 15 per cent at 5 years and 26 per cent at 10 years; with a mean follow-up of 7·4 years, nearly 20 per cent of the series have a permanent stoma and only one patient has died.

Acknowledgements

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Natural history of indeterminate colitis

The long-term outcome of patients with a pathological diagnosis of indeterminate colitis on a colectomy specimen was investigated. The case records of 46 such patients operated on for inflammatory bowel disease between 1960 and 1983 were reviewed. Using the preoperative clinical information, pathological and radiological reports, it was possible to divide the patients into three groups: group 1, probable Crohn's disease (19 cases); group 2, probable ulcerative colitis (11 cases); and group 3, indeterminate colitis (16 cases). The patients were followed for a minimum of 2·5 years (median 10, range 2·5–28 years). During this period the probable diagnosis changed in five cases only. One patient in group 1 (Crohn's disease) was subsequently considered to have ulcerative colitis (group 2). The other four patients were all in group 3. Three were reclassified as ulcerative colitis and the fourth as Crohn's disease on the finding of a single granuloma in a rectal biopsy. No case in group 3 required subsequent small bowel surgery. These data suggest that patients continuing with a diagnosis of indeterminate colitis in spite of careful preoperative and postoperative assessment are unlikely to show features of Crohn's disease in the long term. This may be important when considering a subsequent restorative proctectomy.

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In a proportion of patients undergoing colectomy for inflammatory bowel disease, the pathologist will be unable to make a confident diagnosis of either ulcerative colitis or Crohn's disease on the resected specimen. In many such cases, however, clinical and radiological features together with pre- and postoperative biopsy material can result in patients being allocated to one or other type of inflammatory bowel disease group. However, there still remains a group of patients in whom a definite diagnosis cannot be reached[1], and who are best described by the term 'indeterminate colitis'. The outcome in these patients is uncertain, but is important when considering subsequent surgery and particularly the advisability of restorative protectomy.

Price[2] previously reported on 30 patients with a diagnosis of indeterminate colitis but his was essentially a histopathological paper attempting to place the group within the spectrum of non-infective inflammatory bowel disease. The subsequent clinical course was not considered. Pezim *et al*[3] reported upon the outcome of 25 patients who underwent one-stage restorative proctocolectomy in whom the pathological diagnosis on the resected specimen was indeterminate colitis. All of these patients, however, were thought to have ulcerative colitis before operation. Furthermore, the follow-up of these patients was short, varying from 1 to 78 months. It is therefore not possible, from this report, to comment on the long-term prognosis of patients with a preoperative diagnosis of indeterminate colitis who undergo restorative proctocolectomy.

The aim of the present study was to obtain information on the natural history of indeterminate colitis. A group of 46 patients with a pathological diagnosis of indeterminate colitis, followed for up to 28 years, was studied. Particular attention was paid to the development of features indicating a change of diagnosis to ulcerative colitis or Crohn's disease.

Patients and methods

Between 1960 and 1983, 675 patients underwent colorectal surgery for inflammatory bowel disease at one hospital. In 53 (7·9 per cent) the pathological diagnosis on examining the resected specimen was indeterminate colitis. Among the 53, 40 (75 per cent) were treated by urgent operation compared with 150 (24 per cent) of the remaining 622 cases. In no case was malignancy found in the operative specimen, four of the 53 patients died after surgery and three were lost to follow-up, leaving 46 patients for study. The operations included total proctocolectomy (19), colectomy with ileorectal anastomosis (7), colectomy with ileostomy and preservation of the rectal stump (19), and partial colectomy (1). The deaths after operation all occurred within 16 days of surgery and were due to myocardial infarction (1), pulmonary embolus (1), and overwhelming septicaemia (2). There were 21 men and 25 women with an age range of 15–76 years (median 36 years). All preoperative clinical, pathological and radiological reports were reviewed. On the basis of this assessment it was possible to allocate the patients to three groups: probable Crohn's disease (19), probable ulcerative colitis (11), and indeterminate colitis (16). The patients were followed after operation for periods ranging from 2·5 to 28 years (median 10 years).

Results

Of the 46 patients, 19 were thought to have Crohn's disease. This conclusion was reached as a result of the following observations. Thirteen of the 19 patients had a preoperative history of anal disease including fissure, fistula, abscess, stenosis or skin tag. One patient had a rectal stricture, one a rectovaginal fistula and one a sinus from the rectum to the sacral area. Fourteen of the 19 patients had preoperative radiological studies performed. In 13 the reported appearances and distribution of disease suggested a diagnosis of Crohn's disease rather than ulcerative colitis and there was evidence of ileal involvement in four. Preoperative biopsy material was available in 15 cases. In four granulomas were seen and a confident diagnosis of Crohn's disease was made, and in five the features were reported as suggestive of Crohn's disease. In five the appearances were non-specific, and in one the rectal biopsy was normal.

In 11 patients the diagnosis was considered to be ulcerative colitis. All had a preoperative radiological contrast enema with features entirely consistent with ulcerative colitis. Six of the patients had a preoperative rectal biopsy showing definite

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Table 1 *Preoperative assessment of the 46 patients*

	No. of patients	Anal lesion	Preoperative histology	Preoperative radiology
Probable Crohn's disease	19	13	15: 9 contributory 6 equivocal	14: 13 contributory 1 equivocal
Probable ulcerative colitis	11	2	11: 9 contributory 2 equivocal	11: all contributory
Apparently indeterminate colitis	16	5	10: all equivocal	9: all equivocal

Table 2 *Late mortality and the incidence of large and small bowel surgery during follow-up in the three diagnostic groups*

	Crohn's disease ($n=19$)	Ulcerative colitis ($n=11$)	Indeterminate colitis ($n=16$)	Total ($n=46$)
Late deaths*	5	1	2	8
Further large bowel surgery	7	6	3	16
Further small bowel surgery	3	1	0	4

* Unrelated to inflammatory bowel disease

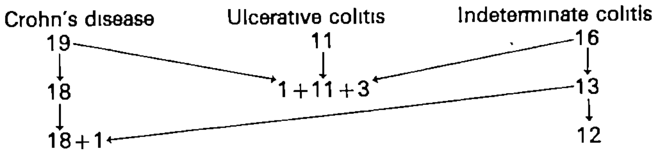

Figure 1 *Change in diagnosis during follow-up period*

ulcerative colitis and in three the biopsy was consistent with this diagnosis In two patients the rectal biopsy showed non-specific inflammation. Although two patients gave a history of a successfully treated anal fistula, in both cases the radiological and histological evidence was strongly in favour of ulcerative colitis.

It was not possible to assign 16 patients to either the Crohn's disease or ulcerative colitis group although in ten there was preoperative biopsy information and in nine a barium enema report. Five patients had a history of an anal lesion including a fissure in three, a fistula in one and an ulcer in one. In each case, however, there were either insufficient specific features of Crohn's disease or ulcerative colitis, or so much overlap was present that a definite diagnosis of one or the other could not be made (*Table 1*)

During the period of follow-up there were eight late deaths among the 46 patients, all unrelated to inflammatory bowel disease. The causes included the following: carcinoma of the oesophagus (1), carcinoma of the bronchus (1), cardiovascular disease (3), chronic renal failure (1), bronchopneumonia (1), and unknown cause (1). Twenty patients required further bowel surgery. In 16 this was a proctectomy for persisting rectal symptoms (including two cases with a failed ileorectal anastomosis). In none of these patients was any malignancy present. In the 11 patients with the rectum still *in situ* no subsequent biopsies demonstrated dysplasia. Four patients required subsequent small bowel surgery, three for Crohn's disease and one for a fistula from the ileostomy in a patient in the ulcerative colitis group. *Table 2* shows that the incidence of large bowel surgery in the three groups was similar but none of the 16 patients with indeterminate colitis required a small bowel operation later.

As a result of further histological material becoming available during the follow-up period, the grouping was altered for five patients. These changes are shown in *Figure 1*. Four of these patients came from the indeterminate group. Three were shown to have ulcerative colitis, two after rectal excision and one after repeated rectal biopsies. One was thought to have Crohn's disease as a single granuloma was seen in a rectal biopsy 6·5 years after operation; this patient has, however, remained completely well for 18 years from the time of surgery with no further evidence of Crohn's disease.

Discussion

In any group of patients with inflammatory bowel disease coming to surgery, some are unable to be diagnosed confidently as having either ulcerative colitis or Crohn's disease. The incidence of so-called 'indeterminate colitis' has been reported as 9–20 per cent[1,2,4]. The present series represented 7·9 per cent of the total operated on for inflammatory bowel disease during the study period. This figure is very similar to that previously obtained from this hospital[2]. Of the 53 patients reported here, 40 underwent urgent operation. It is in this group rather than in patients having elective surgery that a firm pathological diagnosis is more diffucult[5]. Price[2] has emphasized the uncertainties in pathological interpretation of tissue obtained at one phase of the patient's illness.

This study has shown that many cases with indeterminate colitis in the operative specimen can be placed with reasonable confidence into Crohn's disease or ulcerative colitis categories by a review of all available features of the case. The clinical course of those considered to have Crohn's disease or ulcerative colitis in this study is compatible with the anticipated natural history of each condition. Thus, of the 19 felt to have Crohn's disease, three had a subsequent small bowel resection with a pathological report of Crohn's disease in each case. In the probable ulcerative colitis group the single case requiring small bowel surgery had an ileostomy fistula with no specific histological features in the excised distal small bowel. This complication may occur in any ileostomy as a result of poor placing of the sutures when constructing the stoma[6]. The integrity of the Crohn's disease and ulcerative colitis groups is also supported by the fact that only one of the 30 patients had the diagnosis revised subsequently. This emphasizes the value of assessing all features even when a surgical specimen is available.

From this study of 16 patients with indeterminate colitis two main observations can be made. First, a subsequent diagnosis of Crohn's disease is unlikely There was only one such case and the criterion (one granuloma in a rectal biopsy) for moving the patient into the Crohn's disease category was weak. In ulcerative colitis, a single granuloma can occur in a biopsy from the large bowel at a site adjacent to previous surgery and in an ileal reservoir after restorative proctocolectomy (I. C. Talbot, personal communication). Since this patient has remained well for 18 years after operation, it may well be that the diagnosis of Crohn's disease is incorrect. The shift of the three patients from the indeterminate to the ulcerative colitis category would not have influenced any surgical decision on choice of operation. The second conclusion is that subsequent small bowel surgery is unlikely in those with indeterminate colitis Indeed there was not a single instance of this being necessary in the 16 patients.

It would seem therefore that indeterminate colitis behaves more like ulcerative colitis than Crohn's disease and thus all surgical options for the former disease remain open. Pezim *et al*[3] have reported recently on the short-term follow-up of 25 patients with indeterminate colitis having a restorative proctocolectomy. The clinical course in these patients with a mean follow-up of 38 months was similar to that of patients with ulcerative colitis. Although a far longer follow-up period will be necessary, their report supports the present findings. The present results allow two conclusions to be drawn. Firstly, many patients in whom a pathological diagnosis of indeterminate colitis is made on a colectomy specimen can be classified as Crohn's disease or ulcerative colitis by taking all diagnostic features into account. Secondly, the disease affecting the remaining patients seems likely to behave as ulcerative colitis rather than Crohn's disease. These patients are thus suitable for the same surgical options as those with ulcerative colitis, including restorative operations with the construction of an ileoanal pouch anastomosis. It is, however, not possible from this study to comment on the risk of developing dysplasia. All patients had the colon removed on entry to the study and all but 11 lost the rectum during follow-up. There was, however, no case of large bowel malignancy in the series.

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Short note

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Changing pattern of intestinal obstruction in Malaysia: a review of 100 consecutive cases

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The pattern of intestinal obstruction is known to vary in different parts of the world according to local factors. Even within the same country, the aetiology and outcome changes as the society develops. In Malaysia where economic and social development has been progressing rapidly over the past decade, the pattern of intestinal obstruction and operative mortality has changed. This report documents the recent changes compared with those reported 10 years ago[1].

Patients and methods

Between 1 January 1986 and 31 December 1988, 100 consecutive patients over 12 years of age operated on for intestinal obstruction in the Department of Surgery, University of Malaya, were reviewed retrospectively Over the same period there were 32 patients with 39 episodes of subacute or partial obstruction who responded to conservative measures. These patients were excluded All patients were followed for 6 months to 3 years Re-operations in the same patient were not considered separate episodes of obstruction.

Results

Age, sex and racial distribution

The ages of the patients ranged from 13 to 84 years, with 44 patients over 60 years of age. The remaining patients were fairly evenly distributed over the younger age groups There were 63 men and 37 women. Sixty-five patients were ethnic Chinese, 22 Malays, 11 Indians and two others. The mean age of the Malay patients was 42 years with 73 per cent of patients below 50 years of age; that of the Chinese was 58 years with 32 per cent of patients below 50 years of age.

Causes of obstruction

The main causes of obstruction are shown in *Table 1*. There was no significant difference in the causes of obstruction between the different ethnic groups

Types of obstruction and operations

Large bowel obstruction occurred in 27 patients, small bowel obstruction in 56 patients, and 17 patients had multiple sites of obstruction involving both large and small bowel. A total of 126 operations were performed for these 100 patients. The majority of patients (54 per cent) were operated on within 24 h of admission. There was a delay in operation of 72 h or more in 23 patients due to doubtful diagnosis.

Mortality and morbidity

The overall 30-day postoperative mortality was four patients. Two died secondary to anastomotic leakage, one from a myocardial infarct and one from an unknown cause

In contrast with the very low mortality, the incidence of morbidity was high (35 per cent). Late morbidity was found in 26 patients (*Table 2*) The main factors which contributed to the high morbidity are identified in *Table 3*.

Discussion

When compared with our experience in 1976[1], the pattern of intestinal obstruction in the Malaysian society has changed considerably. There was a shift towards patients above 60 years of age from 35 per cent to the present 44 per cent. This correlates well with the increase in life expectancy of the population in general and the greater availability of surgical care. The male preponderance is consistent with series reported from other parts of the world[2–5]. The racial preponderance of the ethnic Chinese group remained the same. Chinese patients accounted for 36 per cent of all admissions but contributed to 65 per cent

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Table 1 *Aetiology of 100 cases of intestinal obstruction*

Gastrointestinal tumours	39
Primary	33
Carcinomatosis	6
Adhesions	35*
Hernia (all types)	25
Volvulus	3
Crohn's disease	3
Intra-abdominal abscesses	2
Meckel's diverticulum	1
Intraluminal bezoar	1
Ileocolic intussusception	1

*Adhesions were found to be co-existing with other pathology in 25 cases

Table 2 *Morbidity of 100 cases of intestinal obstruction*

Early morbidity in 35 patients	
Wound infections:	11
Complete wound dehiscence	3
Postoperative haemorrhage	2
Orthostatic pneumonia	13
Urinary tract infection	6
Organ failures:	
Respiratory failure	8
Cardiovascular complications	4
Acute renal failure	4
Cerebrovascular accidents	2
Severe diarrhoea (short bowel)	2
Septicaemic shock:	5
Anastomotic leakage	5
Intra-abdominal abscess	2
Other complications:	
Difficult fluid electrolyte and acid-base management	5
Hepatitis	2
Diabetic ketoacidosis	1
Arterial embolism to lower limb	1
Delayed complications in 26 patients:	
Recurrent obstruction	14
Malabsorption	3
Chronic abdominal pain	5
Weight loss >5 kg	3
Recurrent carcinoma	7
Others	5

Table 3 *Factors influencing morbidity in 100 cases of intestinal obstruction*

Main factors	No of patients	No. with morbidity	Morbidity rate (%)
Presence of strangulated bowel	22	12	54
Duration of delay in surgery.			
<24 h	54	16	30
24–48 h	13	5	38
49–72 h	10	4	40
>72 h	23	10	43
Type of bowel obstructed:			
Large bowel	27	7	26
Small bowel	56	18	32
Multiple sites	17	10	59

of all patients with intestinal obstruction. The previous report[1] had suggested that the Chinese tend to have a higher incidence of tumours and adhesions[6,7], but we did not find a difference in the aetiology of obstruction between races. Any ethnic difference is probably related to the local socio-economic factors rather than a true ethnic or genetic difference. There was an increase in the Malay population in Kuala Lumpur from 33 per cent in 1980 to 36 per cent in 1988[8]. The increasing rural to urban migration of the Malays as a result of social progress and social restructuring has resulted in a relatively young Malay population in urban areas. As the present urban Malay population ages, and a larger proportion of the Malay population becomes urbanized, this ethnic difference will disappear within the next 10–15 years.

In the aetiology of intestinal obstruction, adhesions and tumours have superseded abdominal hernia as the leading cause of intestinal obstruction This may be related to an increasing incidence of gastrointestinal tumours[9] as well as the reduced importance of hernia as a cause of intestinal obstruction as a result of the increased availability of surgical services in the country. Experience in the West has consistently demonstrated this change[10,11] There was also a decline in the incidence of tuberculosis as a cause of intestinal obstruction. This is explained by the widespread immunization programme and generally higher level of health care.

The mortality of intestinal obstruction has declined from 14 per cent overall to 4 per cent; this improvement is attributed to earlier surgical intervention, more effective pre- and postoperative care, and improvement in the intensive care unit facilities.

Despite this improvement in mortality, our morbidity remained high, although it is in keeping with other series[2,12–14]. The risk factors were similar to other series with strangulation and delay in intervention being the main causes leading to a high morbidity (*Table 3*)[2,5,13,15]. Early detection of the clinical evidence of strangulation and a sense of urgency in operative intervention remain the cornerstones of effective treatment. A further reduction of morbidity and mortality is our challenge.

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Outcome after emergency surgery for cancer of the large intestine

The data for 77 patients with colorectal cancer who underwent emergency surgery for acute intestinal obstruction (57 patients) or perforation (20 patients) within 24 h of admission were evaluated. The patients were older and had more advanced disease than patients undergoing elective surgery for colorectal cancer. Emergency surgery for carcinoma of the right colon consisted of primary resection in 95 per cent of cases and was followed by a 28 per cent mortality rate. Perforated tumours of the left colon and rectum were managed by primary resection in 82 per cent of cases with a 22 per cent mortality rate. In contrast, obstructing tumours of the left colon and rectum were treated by primary resection in 38 per cent of cases with a 6 per cent mortality rate, and by primary decompression in 62 per cent of cases with a 25 per cent mortality rate. The overall postoperative mortality rate was 23 per cent and increased with advanced tumour disease, perforation and peritonitis. Cardiac decompensation and intra-abdominal sepsis were the major causes of death. Although the long-term survival rate following emergency surgery was worse than after elective surgery, improvements in outcome should be achieved by better management of the initial emergency situation.

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About 15 per cent of patients with carcinoma of the large intestine present as surgical emergencies, the great majority with acute intestinal obstruction, perforation at the site of the tumour, or a combination of both when perforation occurs in distended colon proximal to the obstructing cancer. Traditionally, the surgical procedure of choice for these emergencies consisted of an initial decompression of the proximal colon followed by resection after an interval of weeks or months. Over the last two decades, the attitude of most surgeons has changed towards a more aggressive initial approach. Emergency resection for cancer of the right hemicolon is now a generally accepted procedure and a primary ileocolonic anastomosis is performed in almost all of these cases[1–3]. Similarly, discontinuity resection for perforated tumours of the left colon has emerged as a standard surgical procedure[4,5]. Current controversy concerns the treatment of obstructing carcinomas of the distal large bowel. In 1979 a major study demonstrated an improved outcome after primary resection[1]. Since then, primary resection has been performed with increasing frequency. Recent results, however, show no difference in the early outcome between primary and staged procedures[6], and the long-term prognosis may even be worse after primary resection[7].

This study analysed the outcome after emergency laparotomy for obstructing and perforated colorectal cancer in this department between January 1982 and December 1987.

Patients and methods

All patients with malignancies have been computer documented in our department In addition, basic clinical data from all colorectal cancer patients were prospectively collected and registered More detailed information about the clinical course was obtained from hospital records, the follow-up records of the oncology outpatient department, or directly from the patient's general practitioner. Between 1982 and 1987, 923 patients underwent surgical treatment for primary colorectal carcinoma in our institution Emergency laparotomy within 24 h of admission was performed for large bowel obstruction or perforation in 77 (8 per cent) patients All of the other 846 (92 per cent) patients are referred to as elective cases in this study, which analysed the relationship between the variables of age, sex, tumour stage and location, surgical treatment, postoperative morbidity and mortality, and long-term survival The tumour stage was classified using the postsurgical histopathological tumour node metastasis (pTNM) classification of the Union International Contra Le Cancrum[8]

The χ^2 test was applied for statistical analyses of the contingency tables. The survival curves were calculated with the Kaplan–Meier method[9]. The log rank test was used to check for significant differences between the Kaplan–Meier estimates[10].

Results

Patients and tumour characteristics

Of the 77 emergency laparotomies, 57 (74 per cent) were performed for obstruction and 20 (26 per cent) for perforation including five (6 per cent) for a combination of obstruction and perforation. The median age of the patients was 67 years in the elective group, 76 years in the group with obstruction and 79 years in the group with perforation. A third of all emergency laparotomies were performed in patients over 80 years of age (*Figure 1*) The sex distribution was similar in the elective (47 per cent men) and the emergency group (51 per cent men) The incidence of emergency surgery varied with tumour location. Obstruction occurred more frequently in cancer of the descending (19 per cent) and sigmoid colon (12 per cent) than in cancer of the right hemicolon (5 per cent) In contrast, perforation was more frequently found in tumours of the right hemicolon (5 per cent) than in tumours of the descending (2 per cent) or sigmoid colon (2 per cent). Rectal carcinomas rarely presented with large bowel obstruction (3 per cent) or perforation (1 per cent).

Diagnosis

Intestinal obstruction was diagnosed clinically and confirmed by plain abdominal films in all 57 patients. A combined large and small bowel ileus was present in 57 per cent of cases. Five (9 per cent) of the underlying carcinomas had already been diagnosed before emergency admission. In all other cases,

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obstruction was the first presented symptom of colorectal cancer. Digital examination or Gastrografin® enema (Schering AG, Berlin, Germany; 27 investigations) established the diagnosis of cancer in 29 (51 per cent) patients before surgery. Flexible endoscopy had no role in the detection of tumour obstruction. Rigid endoscopy was performed twice and failed to demonstrate both sigmoid lesions. Forty per cent of patients underwent exploratory laparotomy.

All 20 patients with colonic perforation presented with clinical signs of localized (25 per cent) or generalized (75 per cent) peritonitis. Ninety per cent of these patients underwent immediate laparotomy without knowledge of the underlying cancer or further diagnostic workup. A Gastrografin enema was performed in one patient and revealed a sigmoid lesion with retroperitoneal perforation. Another tumour had already been detected before emergency admission. Endoscopy was not performed in these patients with peritonitis. Laparotomy demonstrated perforation at the site of the tumour in 75 per cent of patients and in the distended prestenotic colon in 25 per cent of patients. Free rupture caused diffuse or localized peritonitis in 50 per cent and 25 per cent of patients, respectively. Gross faecal contamination of the peritoneal cavity was apparent in 40 per cent of cases. The rupture was concealed with abscess formation and localized peritonitis in 20 per cent of cases. Five per cent of patients presented with a secondary free rupture of a concealed abscess leading to diffuse purulent peritonitis.

Table 1 compares 'T' and 'N' stages and shows that there were more locally advanced tumours in the emergency group than in the elective group. In addition, distant metastases (M_1) were found in 29 per cent of patients presenting on an emergency basis compared to 14 per cent of the elective patients ($P<0.01$). Non-resected, thus unclassified tumours (pT_xN_x), were usually distant or had distant metastases. These pT_xN_x carcinomas were more frequent in the emergency group than in the elective group (23 *versus* 15 per cent; $P<0.05$).

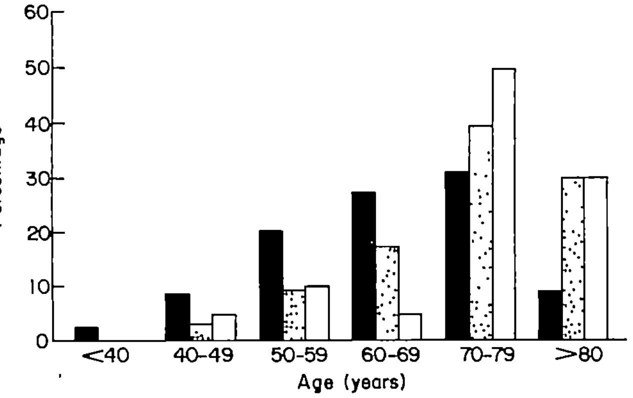


Figure 1 *Age distribution of patients with colorectal cancer* ■, *elective,* ▨, *obstruction,* □, *perforation*

Operative management

Most patients with colorectal obstruction or perforation were admitted to the surgical intensive care unit. All patients were prepared for surgery in a routine fashion including nasogastric suction and adequate resuscitation with crystalloid fluids. The great majority of patients with diversion colostomies were managed without antibiotics. Colonic resection without signs of peritoneal contamination was treated with perioperative antibiotic prophylaxis (cefoxitin or cephazolin). Combination therapy (cefotaxime and metronidazole) was commenced during the operation in all patients with peritonitis and was continued for a minimum of 7 days. All patients were seen and operated on by the senior registrar on call.

The overall resection rate was 85 per cent in the elective group compared with 77 per cent in the emergency group. The resection-for-cure rate, including primary and staged resections, was only 60 per cent in the emergency group compared with 73 per cent in the elective group. The emergency procedures and the operative mortality rate are presented in *Tables 2* and *3*.

Obstructing tumours were treated by primary resection or primary decompression in 49 per cent and 51 per cent of cases, respectively. Of 28 primary resections, 27 were completed with a primary ileocolonic (nine patients) or colocolonic (18 patients) anastomosis. Four of the latter were performed after intraoperative orthograde irrigation, and six were protected by an enterostomy. Primary decompression was followed by

Table 2 *Surgical treatment and postoperative deaths relative to tumour location in patients undergoing emergency treatment*

			Primary decompression	
Emergency situation	Tumour location	Primary resection	Staged resection	Diversion only
Obstruction ($n=57$)	Right hemicolon and transverse colon	11 (3)	1 (1)	–
	Left hemicolon and splenic flexure	17 (1)	11 (0)	10 (5)
	Rectum	–	1 (0)	6 (2)
Perforation ($n=20$)	Right hemicolon and transverse colon	9 (2)	–	–
	Left hemicolon and splenic flexure	8 (2)	–	2 (2)
	Rectum	1 (0)	–	–

Values in parentheses are numbers of deaths

Table 1 *Tumour stage and nodal involvement after resection for elective and emergency colorectal cancer according to the postoperative tumour node metastasis, pTNM, classification*

		Emergency surgery		
Tumour stage	Elective surgery ($n=722$)	Total ($n=59$)	Obstruction ($n=41$)	Perforation ($n=18$)
T_1/T_2 (tumour confined to bowel wall)	33	14*	13	17
T_3 (tumour extending to contiguous structures)	61	81*	81	78
T_4 (tumour extending beyond contiguous structures)	6	5	6	5
N_0 (no nodal involvement)	59	49	42	66
N_1 (regional lymph nodes involved)	34	41	51	17
N_4 (juxta-regional lymph nodes involved)	7	10	7	17

Values are percentages; * $P<0.05$ compared with elective group

Table 3 *Primary resection procedure and postoperative deaths following emergency presentation of colorectal cancer*

	Primary resection		
	With anastomosis		
Emergency situation	One-stage procedure	With protective enterostomy	Without anastomosis
Obstruction	21 (3)	6 (1)	1 (0)
Perforation	6 (2)	2 (0)	10 (2)

Values in parentheses are numbers of deaths

staged resection in 13 of 29 (45 per cent) cases, whereas the initial decompression colostomy was never reversed in the remaining 16 (55 per cent) patients because of postoperative death, non-resectable tumour or distant metastases. All obstructing lesions of the right hemicolon and transverse colon were resected, but only 28 of 38 (74 per cent) of tumours of the left colon and one of seven (14 per cent) of rectal tumours (*Table 2*). Similarly, resection was primary rather than staged in 92 per cent of tumours of the right colon, 45 per cent of tumours of the left colon, and 0 per cent of rectal tumours.

Eighteen of 20 perforated tumours were managed by primary resection; two sigmoid tumours were initially decompressed (*Table 2*). A primary anastomosis was performed in six of nine patients with proximal resections (ileocolonic anastomosis) but only in two of seven distal resections (colocolonic anastomosis with protective enterostomy). The remaining seven distal resections were discontinuity resections (Hartmann's procedures) In addition to tumour location, the extent of peritonitis greatly influenced the surgeon's decision to carry out primary anastomosis. Such an anastomosis was performed in 50 per cent of patients with localized peritonitis, in contrast to 13 per cent of patients with generalized peritonitis, and in none with gross faecal contamination

A special problem was posed by perforation of the obstructed colon proximal to the tumour. Three cases were treated by primary extended resection of both the perforated and the tumour carrying segment. One transverse colon cancer with caecal perforation was managed by transverse resection and caecostomy which was subsequently taken down One patient with a sigmoid cancer and perforation of the transverse colon had a transverse colostomy only.

Early outcome

Medical and surgical complications were frequent after emergency surgery for obstruction (*Table 4*). Anastomotic breaks occurred after one of nine (11 per cent) ileocolonic anastomoses and after two of 18 (11 per cent) colocolonic anastomoses. Relaparotomy was necessary for four other intestinal complications including various problems with the decompression enterostomy. The mortality rate was 14 per cent after 21 one-stage resections, 14 per cent after seven primary resections with anastomosis plus enterostomy or discontinuity resection, and 28 per cent after 29 initial decompessions alone (*Tables 2* and *3*). The mortality rate for all obstructing lesions combined was 21 per cent (*Table 4*). Cardiac failure was the major cause of death and occurred mostly after initial decompression, and in patients with advanced disease with peritoneal and hepatic metastases. Postoperative peritonitis was the second most important complication and resulted in four deaths: three patients died from anastomotic leakage including one leak after appendicectomy for insertion of the orthograde irrigation device; one patient with transverse colostomy developed fatal peritonitis after ischaemic necrosis of the caecum.

In contrast to obstruction, most complications and all deaths after surgery for perforated cancer were due to sepsis (*Table 4*). The mortality rate was 33 per cent after six one-stage resections, 17 per cent after 12 primary resections with anastomosis plus enterostomy or discontinuity resection, and 100 per cent after two decompression procedures (*Tables 2* and *3*). The mortality rate for all perforated lesions combined was 30 per cent. Four patients died from persisting intra-abdominal sepsis. Three of these four patients had advanced cancer with distant intra-abdominal metastases Two of the five patients with the dual complication of obstruction and perforation died after operation: one patient following extended resection and one patient with decompression colostomy who developed an early leak from the oversewn perforation site.

Emergency decompression colostomy (31 cases) for either obstruction or perforation carried a postoperative mortality rate of 32 per cent Only 62 per cent of 22 survivors underwent staged resection which was complicated by two non-lethal anastomotic leaks and one death due to complete wound dehiscence. One-stage resection (27 cases) and primary resection with anastomosis plus protective enterostomy or without anastomosis (19 cases) were associated with a 19 per cent and 16 per cent mortality rate, respectively (*Table 3*). The initial enterostomy was subsequently reversed in only nine (56 per cent) of 16 survivors and this was followed by one non-fatal anastomotic leakage.

The frequency and severity of postoperative complications did not correlate with the patient's age. Similarly, the location of the tumour did not influence the mortality rate which was 29 per cent for tumours of the right colon, 21 per cent for tumours of the left colon, and 25 per cent for tumours of the rectum The tumour stage, however, had an important impact on outcome. When metastases were present, the mortality rate was 50 per cent *versus* a 13 per cent mortality rate among patients with local disease. In addition, the extent of peritonitis influenced the clinical course Postoperative complications occurred in 50 per cent of cases with localized peritonitis and in 75 per cent of cases with generalized peritonitis. All patients with faecal peritonitis developed complications, 50 per cent of which were fatal

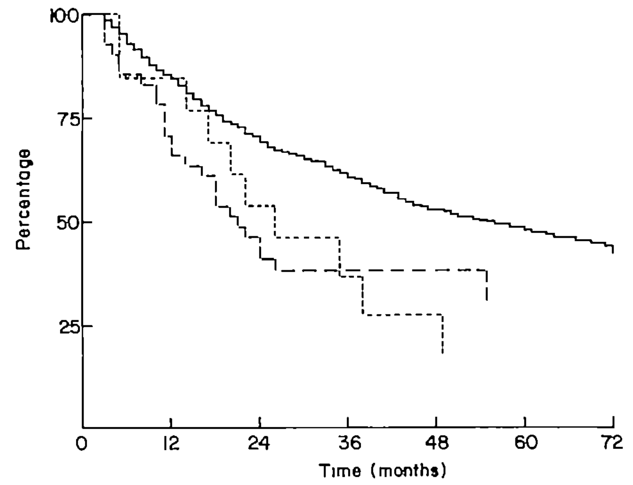
Late outcome

The minimum observation period was 18 months. The prognosis of 31 patients with obstructing or perforated cancer undergoing palliative treatment was very poor: 55 per cent were alive at 2 months, 45 per cent at 6 months, 29 per cent at 12 months and 13 per cent at 18 months. The survival curves after resection for cure in the emergency group and the elective group are shown in *Figure 2*. For better comparison, all deaths occurring within the first 2 months after surgery were excluded. The survival was significantly ($P<0{\cdot}0004$) worse after emergency surgery for obstruction or perforation than after elective resection. Even when patients with comparable tumour size (T_3) or nodal status (N_0) were compared, survival was significantly reduced after emergency surgery ($P<0{\cdot}015$ and $P<0{\cdot}005$, respectively).

Table 4 *Complications within 30 days and resulting death after emergency surgery for colorectal cancer*

Complications	Obstruction ($n=57$)	Perforation ($n=20$)
Wound infection/dehiscence	5	2
Postoperative peritonitis		
Residual peritonitis	1 (1)	4 (4)
With anastomotic insufficiency	4 (3)	1 (1)
Other intestinal	4	1
Pneumonia/respiratory failure	2 (1)	1 (1)
Cardiac failure	10 (7)	3
Total no. of patients	26 (12)	12 (6)
Morbidity rate (%)	46	60
Mortality rate (%)	21	30

Values in parentheses are numbers of deaths



No of patients at risk

Elective	591	548	437	299	202	130	54
Obstruction	31	26	17	10	6	4	2
Perforation	11	10	7	4	3	-	-

Figure 2 *Overall survival curves (Kaplan–Meier estimates) for colorectal cancer following elective surgery (——) or emergency surgery for obstruction (---) or perforation (· ·) Deaths within 2 months of surgery were excluded from the analysis. The numbers indicate the number of patients at risk*

Discussion

The proportion of patients presenting with emergency manifestations of colorectal cancer has remained fairly constant at about 15–20 per cent for obstruction and 3–8 per cent for perforation over the last decades[2,7,11–16]. In our study, only 8 per cent of colorectal tumours required emergency surgery This low incidence may be explained by the referral nature of our hospital practice and, in addition, by the study criterion of surgery within 24 h of admission. It is interesting to note that our emergency cancer patients were about one decade older than the patients in most other studies[3,5,7,12,13,16–18]. They were also much older than the patients undergoing elective surgery, a difference which is often[2,16,18], although not always, found in the literature[7,20].

It is well known that the risk of emergency presentation depends on tumour location. In this series, the relative risk for tumour obstruction increased from the rectum, right colon and sigmoid, to the left flexure and descending colon. In contrast, the relative risk for tumour perforation increased from the rectum and left colon to the right colon.

Emergency presentations occurred more often in patients with advanced disease. Thus the overall resection rate was lower after emergency surgery than after elective surgery (77 *versus* 85 per cent) Similarly, the resection-for-cure rate was reduced after obstruction compared with that after elective surgery (60 *versus* 73 per cent). Resection-for-cure rates of about 50 per cent have also been achieved by others[4,7,16] The resection rate for perforating carcinomas in our series was as high as 90 per cent with a potential for cure in 70 per cent of patients. These figures compare well with resection rates of 66–81 per cent found in the literature[4,14].

Emergency resection followed by primary ileocolonic anastomosis is generally accepted as the treatment of choice for obstructing or perforated tumours of the right colon even in the presence of small bowel distension and peritonitis[1–3] In our experience, emergency ileocolonic anastomosis carried a considerable risk of fatal leakage (20 per cent). Others have reported mortality rates in the range of 16–20 per cent[1,2 21,22] and up to 36 per cent[11,20].

Although primary resection has been performed with increasing frequency for left colon obstruction, many surgeons still advocate staged resection. However, recent reports have failed to demonstrate improved outcome after primary resection as compared with staged resection[1–3], with mortality rates remaining at about 25 per cent. We noted a 6 per cent mortality rate after primary resection *versus* 25 per cent after initial decompression for left colon obstruction. A comparison, however, is inappropriate since the patients were not randomly assigned to one treatment or the other. Kronborg[6] performed the only prospective randomized trial and could not demonstrate a significant difference between the mortality rates after primary (19 per cent) and staged resection (11 per cent).

Another question for continuing debate is whether a primary anastomosis is safe after emergency resection of obstructing cancer of the distal colon. A discontinuity resection avoids the hazard of primary anastomosis[12,23] but the mortality rate after emergency Hartmann's discontinuity resection can be as high as 30 per cent[11]. Primary anastomosis has recently been advocated for selected patients[24]. We performed 18 primary colocolonic anastomoses including six with protective enterostomies followed by two fatal dehiscences and observed an 18 per cent mortality rate which was largely due to anastomotic dehiscence. Ravo[25] has recently developed the intracolonic bypass procedure which excludes the faecal flow, thereby preventing leakage even in the presence of dehiscence. The early experience includes 20 patients with left colon obstruction who underwent primary resection and anastomosis; there was only one death secondary to anastomotic disruption, and no other leaks[25]. These results have to be reproduced by others before the intracolonic bypass procedure can be recommended for the treatment of obstructing cancer. Koruth *et al.*[26] performed primary colocolonic anastomosis after intraoperative antegrade irrigation of the colon with a mortality rate (8 per cent) comparable to that after discontinuity resection (6 per cent). Our first four patients managed with this new technique were included in this analysis; one patient was lost due to complications directly related to the irrigation itself. Others have transferred the concept of emergency ileocolonic anastomosis to lesions of the distal large bowel and have recommended total or subtotal emergency colectomy with ileorectostomy or ileosigmoidostomy[27]. Hughes *et al.*[28] found a low mortality rate of 11 per cent after extended resections which was similar to that after staged resections (6 per cent). In our opinion, this technique should be reserved for patients with the combination of left colon obstruction and perforation of the proximal colon.

The prognosis of patients undergoing palliative procedures for obstruction was very poor. The long-term survival rate of curatively resected patients with obstructing tumour was still lower than that of patients with elective resection for cure. This difference in prognosis was maintained when patients with similar tumour stage were compared. A number of authors[12,17,18,20–22] confirm the reduced prognosis of patients with obstructing cancer. Willet *et al*[29] found that the 5-year survival rate of curatively resected obstructing lesions was only half that of curatively resected elective cases owing to rapid intra-abdominal and systemic spread which suggested a particular biological behaviour of obstructing tumours.

Perforated tumours of the left colon and rectum require emergency eradication of the septic focus, regardless of the location or the extent of peritonitis. Many studies report a decline in mortality rate from 27–73 per cent after staged resection to 8–30 per cent after primary resection[4,14,19,30–32]. In our series, the primary resection rate of 90 per cent was comparable with the 85 per cent rate in elective cases. Our mortality rate of 22 per cent after primary resection compares well with the 15–41 per cent reported in the recent literature (*Table 5*) Primary colocolonic anastomoses are generally not recommended in the presence of peritonitis. We preferred the Hartmann's discontinuity resection, but the postoperative mortality rate was still as high as 20 per cent and was mainly due to intra-abdominal sepsis and, especially, residual

Table 5 *Mortality rates (%) reported in the literature for obstruction and perforation secondary to colorectal carcinoma*

Reference	*n*	Mortality rate (%)
Obstruction		
Glenn and McSherry (1971)[32]	204	13
Peloquin (1975)[17]	127	21
Kronborg *et al.* (1975)[18]	97	14
Dutton *et al.* (1976)[20]	103	16
Irvin and Greaney (1977)[22]	66	38
Raftery and Samson (1980)[15]	101	22
Kelley *et al.* (1981)[13]	156	18
Turunen (1983)[12]	91	15
Umpleby and Williamson (1984)[35]	103	31
Hermanek *et al.* (1985)[19]	173	25
Phillips *et al.* (1985)[2]	713	23
Kronborg (1986)[6]	55	15
Waldron and Donovan (1986)[11]	238	33
Buechter *et al.* (1988)[3]	99	23
Present series	57	21
Perforation		
Glenn and McSherry (1971)[32]	99	15
Welch and Donaldson (1974)[4]	118	30
Peloquin (1975)[17]	59	41
Raftery and Samson (1980)[15]	27	26
Kelley *et al.* (1981)[13]	27	30
Michowitz *et al.* (1982)[14]	42	38
Hermanek *et al.* (1985)[19]	71	31
Present series	20	30

peritonitis. The major determinant for the early outcome is the extent of peritonitis. Our finding of reduced long-term survival after perforation is confirmed by the literature, where the 5-year survival rate of patients with curative resection for perforated cancer is about 20 per cent lower than that of patients with elective surgery for cure[13,15,25,32–34]. Even when perforative tumours were compared with elective cases stage for stage, life expectancy was lower due to increased local, intra-abdominal and distant failure[29].

The rare combination of obstruction and perforation had a particularly sinister prognosis since generalized peritonitis was present in the majority of cases. Our 40 per cent mortality rate is within the reported range of 31–43 per cent[4,5,17,30]. Since the reports from the literature contain only small numbers of these rare cases, a comparison of operative procedures is not feasible. Moreover, a variety of different operations have been performed in the past including colostomy at the site of perforation, resection of the perforated segment followed by secondary resection of the tumour, and subtotal colectomy[5,17,32]. We believe that the treatment of choice is an extended primary resection including the site of tumour and the site of perforation without primary anastomosis.

In conclusion, the problems surrounding emergency presentation continue to be the major determinant of prognosis in patients with obstructing and perforated colorectal cancer. Surgical effort must therefore focus on the emergency situation rather than the underlying oncological problem. Although many deaths are due to medical complications in patients with end-stage cancer, overwhelming abdominal sepsis is still an important cause of death. Safety and control over sepsis are the primary goals and should guide the choice of operative procedure in these older and often frail patients. A variety of operative options have emerged, including the traditional staged approach, the discontinuity resection and the one-stage resection with direct ileocolonic or colocolonic anastomosis. All of these procedures appear to be successful in selected patients and have major disadvantages in others. The continuing challenge of obstructing and perforated cancer is to define the subgroups of patients that might benefit from the different surgical options. Surgical failures have a major impact on outcome and their avoidance will greatly improve the prognosis of patients with emergency colorectal cancer.

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Case report

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Hirschsprung's disease presenting as neonatal gastrointestinal perforation

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In the neonate, Hirschsprung's disease characteristically presents with delayed passage of meconium and/or intestinal obstruction. Intestinal perforation in this age group is more often due to necrotizing enterocolitis or a mechanical obstruction such as atresia or meconium ileus. Hirschsprung's disease, however, may present with intestinal perforation and this association must be recognized promptly if the patients are to be managed appropriately, particularly as half of them have total colonic involvement. Three neonates with Hirschsprung's disease presenting with neonatal intestinal perforation are reported.

Case report 1

A full-term Caucasian male infant who had not passed meconium until 27 h after birth was referred several hours later following the onset of bilious vomiting and abdominal distension. He was promptly resuscitated and underwent examination by a Gastrografin® (Schering Health Care Ltd., Burgess Hill, UK) enema because of the suggestion of meconium ileus from plain radiographic appearances. A normal calibre colon containing little meconium was demonstrated. At operation, an ileal perforation was found 10 cm proximal to the ileocaecal valve. A further 15 cm proximally there was a transitional zone, i.e. a cone-shaped segment between the narrow aganglionic bowel and and the dilated proximal ganglionic bowel. The distal ileum was resected and a proximal ileostomy was fashioned in dilated intestine. The terminal ileum was brought out through the wound as a mucus fistula and rectal suction biopsies were performed.

Subsequent histological examination confirmed that both the rectum and distal ileum were aganglionic but the ileostomy was normally innervated. The infant made an uneventful recovery after operation and successfully underwent a Duhamel pull-through procedure 9 months later. Total colonic aganglionosis was confirmed.

Case report 2

A full-term Asian male infant was transferred at the age of 1 week with a history of failing to pass meconium, progressive abdominal distension and the recent onset of bile-stained vomiting. On arrival, he had clinical and radiological (*Figure 1*) evidence of intestinal perforation with peritonitis. Resuscitation was followed by laparotomy at which a caecal perforation was found in association with a grossly dilated mid-ileum proximal to a collapsed terminal ileum. Seromuscular biopsies from the sigmoid colon were examined by frozen section and confirmed Hirschsprung's disease. The appendix was removed with a cuff of caecum and a proximal ileostomy with distal mucus fistula were fashioned. One week later, when the caecum was reported as aganglionic, a subtotal colectomy and distal ileal resection were performed in order to avoid the potential complications of distal colonic washouts in the presence of a sutured caecal perforation. Histology confirmed total colonic and distal ileal aganglionosis. The patient later required a third laparotomy for intestinal obstruction due to an internal hernia. He then thrived and underwent a successful Duhamel pull-through procedure at the age of 7 months.

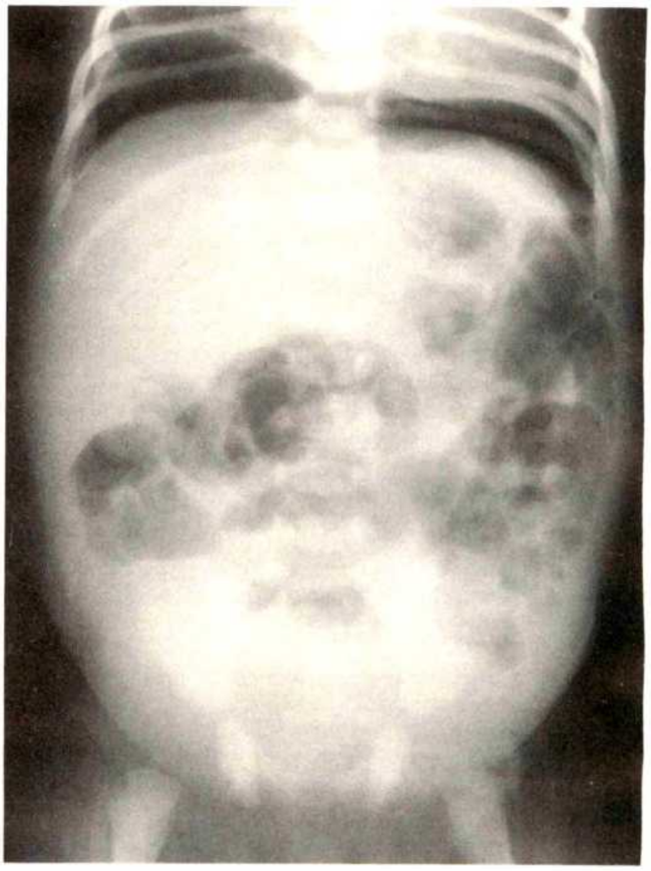

Figure 1 *Plain abdominal radiograph of a neonate (case 2) demonstrating a pneumoperitoneum secondary to a caecal perforation from Hirschsprung's disease*

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Table 1 Summary of reported cases of Hirschsprung's disease presenting with neonatal intestinal perforation

Site of perforation	Total no. of patients	TCA	Proximal	Distal	Unknown
Terminal ileum	5 (9)	5	0	0	0
Appendix	6 (11)	3	2	0	1
Caecum/ascending colon	40 (70)	18	7	13	2
Splenic flexure	3 (5)	1	0	1	1
Sigmoid colon	3 (5)	0	0	3	0
Total	57 (100)	27 (47)	9 (16)	17 (30)	4 (7)

Values in parentheses are percentages. TCA, total colonic aganglioslis; proximal, site of transition zone proximal to splenic flexure, distal, site of transition zone between splenic flexure and rectum

Case report 3

A female Caucasian infant born at 35 weeks gestation was referred at the age of 30 h having failed to pass meconium and with clinical and radiological evidence of a pneumoperitoneum. A multicystic right kidney had been diagnosed antenatally and extra digits were noted. Chromosome studies revealed a normal female karyotype. She required intensive resuscitation including intubation and ventilation before laparotomy. At operation, a caecal perforation with meconium peritonitis was managed by a limited right hemicolectomy and construction of proximal and distal stomas Histological examination demonstrated aganglionic large bowel in continuity with 0 5 cm of aganglionic ileum. The infant made a gradual recovery after operation but has since undergone a further laparotomy for adhesive intestinal obstruction at which a subtotal colectomy and revision of ileostomy were performed She is currently awaiting definitive surgery for Hirschsprung's disease.

Discussion

Hirschsprung's disease rarely presents with intestinal perforation but if this occurs it is most often in the neonatal period[1]. In Swenson and colleagues' review of 501 patients with Hirschsprung's disease treated over a 26-year period, 16 (3·4 per cent) presented with intestinal perforation, all of whom were neonates[2]. Published reports of neonatal Hirschsprung's disease presenting with neonatal intestinal perforation[1–8] together with our own three patients provide a total of 57 cases (*Table 1*). Several important conclusions emerge from analysis of these data.

Ninety per cent of the perforations were in the proximal colon, appendix or terminal ileum Total colonic aganglionosis represents approximately 8 per cent of patients with Hirschsprung's disease[9] but was the underlying diagnosis in half of those presenting with neonatal intestinal perforation and accounted for almost all of the cases presenting with appendiceal or ileal perforations. In general, both short and long segment Hirschsprung's disease may be complicated by perforation in ganglionic bowel whilst in total colonic disease the perforation is in aganglionic bowel. The mechanism of perforation may be related to increased intraluminal pressure There are only two cases in the literature that have been specifically associated with enterocolitis[4,7] and none of our cases demonstrated clinical or histological features of enterocolitis.

Hirschsprung's disease accounts for only 5–8 per cent of neonatal ileocolic perforations overall, the vast majority arising as a consequence of necrotizing entercolitis[5,8]. The surgeon should also consider meconium ileus, meconium disease of prematurity and intestinal atresias However, Hirschsprung's disease must be considered if there is no intramural gas typical of necrotizing enterocolitis or if there is an isolated appendiceal or caecal perforation[3,10].

If Hirschsprung's disease is not recognized as a potential cause of neonatal intestinal perforation, the consequences may at best be a troublesome aganglionic stoma and at worst fatal[3,7,10]. Because proximal perforations more often occur in aganglionic bowel, exteriorizing this segment as a stoma is likely to lead to continuing obstruction and a consequently higher risk of entercolitis. A careful search for a transiton zone should be made in suspected cases in order to site the stoma appropriately. Ideally, facilities for intraoperative frozen section examination of intestinal biopsies should be available to ensure that the stoma is ganglionic. Failing this, a proximal stoma should be sited in dilated bowel and urgent histological examination of a rectal suction biopsy, the appendix or other resected bowel and a biopsy from the stoma should be made.

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Non-steroidal anti-inflammatory drugs and complicated diverticular disease: a case–control study

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Fifty patients with severe complications of diverticular disease were compared with two groups of 50 controls, matched for age and sex. The first control group (A) was randomly selected from all emergency hospital admissions, and the second group (B) from patients with uncomplicated diverticular disease. Of the 50 study patients, 24 (48 per cent) were taking non-steroidal anti-inflammatory drugs (NSAIDs) at the time of admission compared with nine (18 per cent) of control group A and ten (20 per cent) of control group B. Both of these differences were statistically significant, indicating a strong association between the ingestion of NSAIDs and the development of severe complications of diverticular disease.

Non-steroidal anti-inflammatory drugs (NSAIDs) are well known to injure the gastric and duodenal mucosa[1–3], but it is becoming increasingly clear that both the small bowel and the colon are also vulnerable[4,5]. In this study, we have investigated the role of NSAIDs in the development of the complications of diverticular disease, using a case–control approach.

Patients and methods

Twenty-five men and 25 women admitted to Aberdeen Royal Infirmary with severe complications of diverticular disease between 1983 and 1988 were compared with two groups of age- and sex-matched controls admitted during the same period. Severe complications were defined as pericolic abscess, generalized peritonitis, bleeding requiring surgical intervention and fistula formation The first control group (A) was chosen from 1000 randomly selected emergency hospital admissions by matching each study patient with the first available control patient of the same age and sex The second control group (B) was similarly acquired from a list of patients in whom a diagnosis of painful but uncomplicated diverticular disease had been made by barium enema or colonoscopy

Patients were excluded from the study if an adequate drug history was not available from the case notes, but the groups were otherwise consecutive Medication on admission to hospital was recorded for each patient and the groups were compared with regard to intake of NSAIDs

Results

Of all the patients, in both study and control groups, a total of 43 were on NSAID therapy at the time of admission to hospital. The range of drugs which were being taken is shown in *Table 1*, and the indications for treatment are given in *Table 2* In the study group, complications comprised pericolic abscess (19 cases), generalized peritonitis (23 cases), severe bleeding (five cases) and fistula formation (three cases). The mean age was 64 years (range 20–93 years).

Of the 50 study patients, 24 (48 per cent) were taking NSAIDs compared with nine (18 per cent) in control group A and ten (20 per cent) in control group B (*Table 3*). Using control group A, the estimated odds ratio for patients with complicated diverticular disease being on NSAIDs was 4·0 with a 95 per cent confidence interval of 1·46–13·64 ($P<0{\cdot}01$). When control group B was used, the odds ratio was 3·80 with a 95 per cent confidence interval of 1·37–13·03 ($P<0{\cdot}01$).

Discussion

NSAIDs are thought to damage the gastrointestinal mucosa in part by inhibiting prostaglandin synthesis[6] and, although the upper gastrointestinal tract is at high risk owing to the intraluminal presence of the drug, systemic effects are also important and the colon may be particularly susceptible to them. Certainly, fenamate intake is associated with mild colitis[7], and other NSAIDs can occasionally cause an ulcerative

Table 1 *Range of non-steroidal anti-inflammatory drug preparations used in patients with complicated diverticular disease (study group) and controls (group A, random emergency hospital admissions, group B, uncomplicated diverticular disease)*

NSAID	Study group	Control Group A	Control Group B	Total
Aspirin	2	1	2	5
Azapropazone	1	0	0	1
Benorylate	0	0	1	1
Diclofenac	7	1	0	8
Diflunisal	1	0	0	1
Fenbufen	1	0	2	3
Fenoprofen	1	0	0	1
Flurbiprofen	1	1	0	2
Ibuprofen	1	2	1	4
Indomethacin	2	2	1	5
Mefenamic acid	3	0	2	5
Naproxen	3	2	1	6
Piroxican	1	0	0	1

Table 2 *Indications for non-steroidal anti-inflammatory drug therapy in patients with complicated diverticular disease (study group) and controls (group A, random emergency hospital admissions, group B, uncomplicated diverticular disease)*

Condition	Study group	Control Group A	Control Group B	Total
Osteoarthritis	11	2	4	17
Cervical spondylosis	2	0	0	2
Musculoskeletal pain	0	2	1	3
Dysmenorrhoea	2	0	0	2
Polymyalgia rheumatica	2	0	0	2
Rheumatoid arthritis	1	1	1	3
Frozen shoulder	1	0	0	1
Gout	1	0	0	1
Cardiovascular	1	0	0	1
Not known	3	4	4	11

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Table 3 *Comparison between patients with severe complications of diverticular disease (cases) and two age- and sex-matched control groups (A, random emergency hospital admissions, B, uncomplicated diverticular disease)*

On NSAIDs	Cases compared with control	
	Group A	Group B
Case and control	4	5
Case only	20	19
Control only	5	5
Neither	21	21
Odds ratio	4·0	3·80
95 per cent confidence interval	1·46–13·64	1·37–13·03
P value	<0·01	<0·01

NSAIDs, non-steroidal anti-inflammatory drugs; *P* values calculated using McNemar's test for paired binary data

proctitis or colitis[8]. There have also been several reports of large bowel perforation and ulceration[9–13], although the significance of these isolated findings is unclear. In a retrospective study of 268 cases of colonic or small bowel perforation or haemorrhage, it was found that the patients were more than twice as likely to be taking anti-inflammatory drugs (including steroids) than were age- and sex-matched controls[14], and in a recent study of patients with complicated diverticular disease there was a strong association between corticosteroid or NSAID intake and the most serious complications[15].

In this case–control study, we have found that more patients with complicated diverticular disease were taking NSAIDs than were randomly selected emergency hospital admissions or patients with uncomplicated diverticular disease. It could be argued that severe abdominal pain might increase the likelihood of NSAID intake, but, as can be seen from *Table 1*, most of the patients in the study group were being treated for definite conditions unrelated to the presenting complaint. In any case, it is unlikely that NSAIDs would be prescribed for abdominal pain in view of their known effects on the stomach and duodenum. It is also conceivable that the disease might have biased the accuracy with which the drug history was taken. This we have tried to minimize by using control patients who were admitted as emergencies, or who had painful diverticular disease.

It is interesting to note that the percentage of patients in our study who were taking NSAIDs (48 per cent) is very similar to the 42 per cent of patients with upper gastrointestinal bleeding reported by Bartle *et al.*[16]. This indicates that complicated diverticular disease may be as commonly associated with NSAID ingestion as is gastroduodenal haemorrhage, and that appropriate caution should be exercised. Clearly, diverticular disease alone cannot be taken as an absolute contraindication for NSAIDs, but a good reason for prescribing such drugs must be present in patients with this condition.

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Role of intraoperative enteroscopy in obscure gastrointestinal bleeding of small bowel origin

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Intraoperative enteroscopy was performed in 12 patients (median age 68 years) with obscure gastrointestinal bleeding probably of small bowel origin, six of whom were men. All the patients were evaluated by routine haematological, coagulation and biochemical profiles, upper and lower gastrointestinal endoscopies, visceral angiography and/or isotope scanning. All the patients were anaemic. Visceral angiography was useful on three of the 12 occasions on which it was used and isotope scanning was valuable on eight of the 11 occasions it was used. Nine patients had undergone previous laparotomy. Enteroscopy was performed successfully in all cases, with fresh blood and discrete vascular lesions being the chief findings (10 of 12 cases). Segmental resections (n = *8) and local resections* (n = *2) were performed in ten patients, with two patients having more than one laparotomy for rebleeding. Five patients developed postoperative complications and there was an operative death and one late death. Three of the ten surviving patients experienced further rebleeding. Intraoperative enteroscopy is now an essential adjunct to laparotomy for gastrointestinal bleeding which has been localized to the small bowel before operation.*

Obscure gastrointestinal bleeding resulting in acute or chronic blood loss continues to pose a major diagnostic challenge worldwide[1–5]. Bleeding from the small intestine accounts for a small percentage of gastrointestinal haemorrhage, with vascular malformations, small bowel tumours, ulcers (both inflammatory and ischaemic), and Meckel's diverticulum being the common causes. The diagnostic value of preoperative localizing studies, including upper and lower gastrointestinal endoscopy, nuclear scanning and selective visceral angiography is contentious[3,6,7]. The introduction of intraoperative enteroscopy means that it is now possible to visualize the entire gastrointestinal tract from mouth to anus[3,5,8]. This report summarizes our experience with intraoperative enteroscopy in the management of patients with obscure bleeding localized to the small intestine.

Patients and methods

Over a 5-year period from 1985 to 1989, 60 patients with obscure gastrointestinal bleeding were referred to the Hammersmith Hospital The records of 26 patients, with bleeding arising from the small intestine, were reviewed. Twenty-two patients had bleeding localized to the small intestine, detected either by isotope scanning using ^{99m}Tc-labelled sulphur colloid, or ^{99m}Tc-labelled red blood cells, or by visceral angiography. From this group, 18 patients proceeded to laparotomy, during which 12 underwent on-table enteroscopy. The remaining four patients with negative preoperative localization studies underwent laparotomy and resection of small bowel lesions. This report describes our experience with on-table enteroscopy performed in the 12 patients with preoperative localization of bleeding to the small intestine

All the patients had been extensively investigated elsewhere with multiple endoscopies, barium contrast studies, angiography and isotope scans. Routine haematological, biochemical and coagulation profiles were obtained. The investigative routine included upper and lower gastrointestinal endoscopies, isotope scanning with either ^{99m}Tc-labelled sulphur colloid or ^{99m}Tc-labelled red blood cells and visceral angiography Before laparotomy, mechanical cleansing of the bowel was obtained with sodium picosulphate (Picolax®, Nordic, Feltham, UK) and solid food restriction.

At laparotomy, adhesiolysis was performed with particular care, to avoid creating any iatrogenic lesions which could be mistaken at endoscopy for vascular malformations. This was followed by meticulous examination of the bowel, looking in particular for tumour, mucosal or submucosal nodules or abnormal vasculature.

Enteroscopy technique

Operative enteroscopy was performed using a Pentax (Tokyo, Japan) FC38LH colonoscope, which has a working length of 160 cm. Once the instrument passed the pylorus it was gently guided along the duodenum by the first assistant until it had negotiated the duodenojejunal flexure The small bowel was then examined segmentally, with an occlusion clamp lightly applied at fixed distances from the duodenojejunal flexure to prevent overdistension of the more distal bowel It is essential to examine the mucosa as the endoscope is being advanced and to aspirate the inflated segment thoroughly but gently before progressing distally.

The endoscopic appearances were classified as normal, or abnormal. Abnormalities seen were the presence of discrete red spots with a fern-like margin, and the presence of fresh blood coating the mucosa or melaena Endoscopic appearances were supplemented by simultaneous viewing from the outside of the transilluminated bowel wall Normal vascular patterns were readily recognized Abnormalities seen on transillumination were also assessed internally to distinguish vascular lesions from any haematomas caused by operative trauma.

The term segmental resection is used to denote resection of a segment of intestine and mesentery: local resection implies local removal of a full thickness piece of bowel only

Results

The clinical details are summarized in *Table 1* There were six men and six women whose ages ranged from 45 to 83 years (median 68 years) The length of history varied from 2 months to 6 years. At presentation, eight patients had frank melaena, and six had iron-deficiency anaemia, while all had stools which tested positive for the presence of occult blood.

All the patients were anaemic (haemoglobin < 10 g/100 ml) while six were hypoalbuminaemic (albumin < 34 g/100 ml). Only one patient had abnormal coagulation (International normalized ratio, INR = 5), as she was on warfarin therapy

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Table 1 *Clinical details, operative enteroscopy findings, surgical procedure, and clinical outcome*

			Enteroscopy finding				Surgical procedure				
Case	Age/Sex	Previous laparotomy	Fresh blood	Vascular lesion	Melaena	Normal	Local resection	Segmental resection	Nil	Complication	Rebleed
1	62/M	–	+					+		–	–
2	45/M	–	+					+		–	–
3	65/F	–				+	+			–	+
4	67/M	Subtotal colectomy	+(2)					+(2)	+	–	Asymptomatic
5	67/F	Anterior resection	+					+		Chest infection	–
6	68/F	No surgical procedure	+				+	+			Asymptomatic
7	68/M	Right hemicolectomy		+			+			Stress ulcer	Died
8	72/M	Jejunal resection		+				+		–	–
9	80/F	Subtotal colectomy	+					+		Ileus, chest infection	–
10	81/M	Right hemicolectomy		+				+		Chest infection	Rebleed (died)
11	82/F	Right hemicolectomy	+					+			Angiodysplasia in duodenum, oesophagitis with duodenitis
12	83/F	No surgical procedure			+			+		Reactionary haemorrhage	+

because of a prosthetic aortic valve. Two patients had chronic renal failure and one had mitral incompetence.

Before operation, all the patients had bleeding localized to the small intestine either by isotope scanning or visceral angiography Visceral angiography was performed on 12 occasions in ten patients, as an emergency procedure ($n=6$), showing extravasation of contrast into a jejunal loop in one case only, and electively ($n=6$) showing caecal angiodysplasia in one case and jejunal and colonic malformations in another. Isotope scans using ^{99m}Tc-labelled sulphur colloid ($n=3$) or ^{99m}Tc-labelled red blood cells ($n=11$) were more useful. Three examinations were normal, with abnormal appearance of the jejunum ($n=8$), ileum ($n=2$) or duodenum ($n=1$) being seen in the remainder. Nine patients had undergone laparotomies elsewhere before referral to the Hammersmith Hospital.

On-table enteroscopy was performed orally in ten cases, and *per rectum* and through an enterotomy in one case each. In all cases of oral enteroscopy it was possible to reach mid-ileum only, as adhesions from previous laparotomies resulted in tethering in the mesentery. The endoscopic findings were fresh blood ($n=7$) and discrete vascular lesions ($n=3$) in the proximal jejunum, melaena ($n=1$) in the distal jejunum and ileum and no lesion ($n=1$). Segmental resections of the proximal 25 cm of jejunum were performed as a primary procedure in eight patients as were local resections in two patients. The remaining two patients (cases 4 and 6; *Table 1*) had more than one laparotomy for rebleeding and are now asymptomatic.

The postoperative complications included chest infections ($n=3$), paralytic ileus ($n=1$), a reactionary haemorrhage from mesenteric bleeding necessitating a re-laparotomy ($n=1$) and haematemesis caused by stress ulceration ($n=1$). There was one operative death from a chest infection leading to septicaemia, and one late death that occurred in the patient with chronic renal failure.

Histological examination of the resected specimens revealed typical angiodysplasia ($n=2$), an ischaemic ulcer with underlying congested vessels ($n=2$), haemangioma ($n=1$), a mucosal ulcer with an eroded vessel in its base and fresh blood in the submucosa ($n=1$), mucosal ulceration with clusters of thin walled dilated vessels in submucosa ($n=1$), and an arteriovenous malformation ($n=1$). Four cases were normal, evaluated at a time when we did not use the barium gelatin or silicone rubber injection techniques[9,10].

Duration of follow-up ranged from 2 months to 5 years (median 6 months). Excluding the two patients who underwent more than one laparotomy for recurrent bleeding, three patients have had rebleeds. One of these patients underwent segmental resection of her proximal jejunum, in spite of a normal endoscopic appearance, as a preoperative ^{99m}Tc-labelled red blood cell scan strongly suggested a proximal small bowel bleeding site. She has bled on two separate occasions since her laparotomy and is being managed conservatively. Another patient was on anticoagulants for a prosthetic aortic valve. At the time of laparotomy, although only melaena was detected at enteroscopy, local resection of two suspicious areas was carried out. However, histology revealed normal mucosa She rebled 1 month after surgery and is currently being managed medically. The third patient rebled 3 months following jejunal resection for localized jejunal ulceration and submucosal haemorrhage. At upper gastrointestinal endoscopy, angiodysplastic lesions were treated by diathermy in the third part of the duodenum on two occasions with successful outcome

Discussion

Patients with obscure gastrointestinal bleeding do not have an identifiable source of blood loss despite exhaustive testing, which includes standard radiological or endoscopic investigation, or both, of the upper and lower gastrointestinal tract[11] In spite of a vast array of investigative techniques at our disposal, this condition continues to pose a major diagnostic challenge Accurate localization of bleeding from the small bowel is even more difficult, because of its relative inaccessibility to non-operative endoscopy and its lack of fixation which makes the site of bleeding hard to detect both before and after operation[12]. Only direct visualization of bleeding at endoscopy or surgery, or extravasation of contrast material at angiography, provides unequivocal evidence that a lesion is responsible for bleeding[2].

All of our patients were extensively investigated elsewhere, with nine of our patients (75 per cent) having had previous laparotomies, an experience similar to that of other authors[1,3,6,13]. Accurate preoperative localization of the site of small bowel bleeding is thus of vital importance. All the patients referred to us have upper and lower gastrointestinal endoscopies performed routinely. A normal upper and lower gastrointestinal endoscopic examination limits the site of bleeding to the small bowel. Either an isotope scan, using ^{99m}Tc-labelled red blood cells or ^{99m}Tc-labelled sulphur colloid, or selective visceral angiography is the next investigation performed by us, depending on an assessment of the rate of blood loss. Isotope scans using either Tc-labelled sulphur colloid or ^{99m}Tc-labelled red blood cells are widely used for the detection of gastrointestinal bleeding[14–16]. Our own experience, like that of Bunker *et al.*[17], is that because blood loss is intermittent, ^{99m}Tc-labelled red blood cells are the more effective agent as the tracer stays longer in the vascular bed whereas colloid is rapidly cleared. Imaging the site of blood loss in the small bowel presents problems both because of variable small bowel anatomy and the rapid transit of labelled blood in the lumen. Isotope scans can provide only very imprecise information regarding the site of bleeding; nevertheless they proved invaluable in our patients, in the majority of whom angiography had been unrewarding.

Visceral angiography has proved a useful investigative tool in obscure gastrointestinal bleeding, both in the acute and chronic occult situation[18,19]. Diagnostic angiographic features include extravasation of contrast, which is conclusive proof of bleeding, and the specific appearances of vascular lesions. Preoperative angiography has been reported to be helpful in the diagnosis of small bowel angiodysplasia in 51 per cent and 100 per cent of patients[5,11], although we found it to be unequivocally helpful in only one patient who demonstrated extravasation of contrast, an experience similar to that of Flickinger *et al*[3].

Preoperative localization tests include enteroscopy[1], the fluorescein string test[2] and the use of a long tube[13]. The vast majority of patients will, however, need laparotomy with intraoperative localization of the bleeding source. Although P_{O_2} venous differences[20], methylene blue injection[21] and intraoperative angiography[12] have all been used to localize vascular lesions in the small bowel, we rely on intraoperative enteroscopy to localize the bleeding site accurately. Our technique is similar to that described in the literature[3,5] with the exception of applying occlusion bowel clamps to prevent overdistension of distal gut. Provided careful note is made of the site of clamp application, false-positive results from iatrogenic intramural vascular lesions can be avoided and excellent visualization of the distended bowel segment is obtained. The endoscopic appearance of angiodysplasia is a sharply delineated red mucosal lesion with a flat or slightly raised surface and a round or stellate shape with a fern-like margin[22]. These typical lesions were seen in only three of our patients. The commonest endoscopic appearance in our experience, however, was the presence of fresh blood. The importance of this finding, we feel, has been ignored in descriptions of small bowel enteroscopy in the literature Our surgical policy is to perform a limited (25 cm) proximal jejunal resection, including the duodenojejunal flexure, on the basis of this endoscopic appearance of fresh blood in the absence of a discrete vascular lesion. We feel that a positive identification of a bleeding area in a segment of bowel in the absence of discrete vascular lesions is sufficient grounds for undertaking a segmental resection. Local resections were reserved for excision of definite or dubious vascular lesions. Our positive histology rate of 66 per cent is disappointing, but injection of hot barium gelatin or silicone rubber into the jejunal vasculature is difficult because of the small size and profusion of vessels.

Rebleeding, which occurred in five of our cases, with a successful outcome following re-laparotomy in two patients, can be caused by incomplete resection of angiodysplasia, inappropriate resection of the angiodysplastic lesion when another lesion is responsible, and the development of angiodysplasia in another part of the intestine years after the original surgical resection[23]. Of the three patients who rebled, no bleeding was observed at enteroscopy in two and the blind segmental and limited resections performed probably missed the actual site responsible for the bleeding. The remaining patient, who had a jejunal vascular lesion resected, developed further lesions in the duodenum Rebleeding rates following surgery for colonic angiodysplasia vary from 5 to 37 per cent[10,23,24]. Although there have been reports of excellent results following resection of small bowel angiodysplasia[5,13], a 40 per cent rebleeding rate has been reported in another series[25].

Patients with gastrointestinal bleeding arising from the small bowel form a difficult subgroup of patients with obscure bleeding. Not only is preoperative localization difficult, but adhesions from previous laparotomies make careful adhesiolysis mandatory. A small bowel site of bleeding, on the basis of isotope scans or visceral angiography, in all our patients, necessitated intraoperative enteroscopy. Fresh blood seen on the mucosa at enteroscopy appears to be a good localizing sign. Extravasated blood seen on isotope scanning is less precise, being seen either at or distal to its mucosal source. Although the upper jejunum is a common site for bleeding lesions, the third and fourth parts of the duodenum must not be overlooked. Resection of this area is technically demanding, and lesions localized therein may be the cause of some surgical failures, when only jejunal resection has been performed. A blind proximal jejunal resection is indicated only in the presence of unequivocal preoperative localization of bleeding to the proximal jejunum and negative enteroscopy, in an elderly, poor-risk patient.

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Announcement

The British Journal of Surgery Society
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The Council of the British Journal of Surgery Society is offering up to three European Fellowships to be taken up during 1991. Fellowships are designed:

1) to allow a British surgeon to visit a surgical centre or centres of his/her choice within Europe for a period of 4–6 weeks.
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Risk of peritonitis and fatal septicaemia and the need to defunction the low anastomosis

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The aim of this study was to investigate the need to defunction the low anastomosis after anterior resection of the rectum with total mesorectal excision for rectal cancer. Two hundred consecutive patients (125 defunctioned, 75 non-defunctioned) undergoing low anterior resection for carcinoma were included in the study. Peritonitis requiring emergency laparotomy occurred in 8 per cent of the patients who did not have a defunctioning stoma compared with less than 1 per cent of those patients who had a defunctioning stoma ($P<0{\cdot}01$)*. There was no mortality related to closure of the stoma but seven patients developed a faecal fistula and ten developed an incisional hernia. Despite current trends to avoid the defunctioning stoma, these results suggest that after total mesorectal excision the faecal stream should be temporarily diverted away from the anastomosis that is 6 cm or less from the anal verge to protect against potentially life-threatening anastomotic leakage.*

The Colorectal Research Unit at Basingstoke has followed a consistent policy of regarding low anterior resection with total mesorectal excision as the operation of choice for rectal carcinoma. A 10-year audit of 200 consecutive anterior resections by one of the authors (R.J.H.) revealed a 3 per cent local recurrence rate in 160 operations classed as 'curative' and this suggests a high probability of real benefit from this technique both in terms of local control and long-term cure[1,2]. Abdominoperineal excisions have been substantially reduced and now account for 9·8 per cent of all cases[2].

This paper addresses the adverse consequences of combining lower anastomosis with wider local clearance, a refractory problem of anastomotic leakage. Anxiety about this hazard has alternated with peer pressure against the use of the defunctioning colostomy[3,4] to produce an inconsistent policy regarding faecal diversion. No attempt has been made to analyse the causes of anastomotic leakage, but rather the effect on the outcome of the decision to defunction has been studied.

Patients and methods

Two hundred consecutive patients (114 men, 86 women; mean(s.d.) age 67(12) years) who had undergone stapled low anterior resection for rectal carcinoma were studied with respect to anastomotic integrity. All operations were performed personally by R.J.H. or under his supervision. The technique for anterior resection in this series has previously been described[1,5,6]. The splenic flexure was used for reconstruction in 157 (78·5 per cent) patients and the sigmoid colon in 43 (21·5 per cent). In 95 per cent of patients the anastomosis was constructed using a double purse-string technique, in the remainder a cross-stapling device was used with the EEA® (US Surgical Corporation, East Norwalk, Connecticut, USA) premium gun. In 168 (84·0 per cent) patients the anastomosis was 6 cm or less from the anal verge, in the remaining 32 (16·0 per cent) patients the anastomosis was more than 6 cm but less than 12 cm from the anal verge. The mean(s.d.) anastomotic height in the entire series was 5·1(2·0) cm.

A group of 125 patients (75 men, 50 women; mean(s.d.) age 67(11) years) had a defunctioning loop colostomy. All of these patients had a water-soluble contrast enema to check the integrity of the anastomosis before planned closure of the colostomy (usually 6–8 weeks after the original surgery).

Another group of 75 patients (39 men, 36 women, mean(s.d.) age 67(13) years) underwent stapled low anterior resection without a defunctioning stoma. These patients included only those considered by the surgeon to be at minimal risk from anastomotic disruption. They had good pelvic haemostasis, an excellent colonic blood supply, good bowel preparation and were fit. This group did not have routine radiological assessment of anastomotic integrity, but patients did undergo iopamidol (Niopam®, E. Merck Ltd., Alton, UK) contrast studies if their clinical progress was imperfect.

The progress after operation of all patients was recorded using a computerized system of clinical audit. Particular reference was made to the incidence and consequences of anastomotic leakage in the two groups of patients studied.

Results are expressed as mean(s.d.) and compared between groups by using either the unpaired two-tailed t test or the χ^2 test where appropriate.

Results

Defunctioned group (n = *125*)

In this group 118 patients had an anastomosis at 6 cm or lower, and seven had an anastomosis higher than 6 cm, up to a maximum of 12 cm from the anal verge. Overall the mean(s.d.) anastomotic height was 4·5(1·5) cm.

One patient (0·8 per cent) in this group, whose anastomosis was less than 6 cm from the anal verge, developed faecal peritonitis which necessitated an emergency laparotomy. At operation it was apparent that a faecal column persisted in a poorly prepared bowel proximal to the anastomosis. Peritoneal toilet and irrigation of the distal colon were undertaken. After an initially good recovery, the patient died from a cerebrovascular accident 30 days after this second laparotomy.

Twenty-one (16·8 per cent) patients in this group showed radiological evidence of anastomotic leakage. In 20 patients the anastomosis was 6 cm or less from the anal verge. In 15 patients the defect in the anastomosis remained asymptomatic and healing occurred after deferring colostomy closure for a further 1–4 months. The remaining six patients included one who healed rapidly after an examination under anaesthesia to remove a retrorectal concretion of stool, two in whom advancing local malignancy was thought to be contributing to the anastomotic disruption, and two who died before closure. One patient with obvious colonic ischaemia developed chronic pelvic sepsis, eventually requiring excision of the 'neorectum' 5 years after the initial operation.

One hundred and twenty stomas have been successfully closed with no mortality. However, closure of the loop colostomy was associated with seven faecal fistulae, all of which closed spontaneously. Ten patients have subsequently developed an incisional hernia.

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Table 1 *Chronological details of five patients who developed faecal peritonitis due to anastomotic failure*

Patient no.	Sex	Age (years)	Dukes' classification	Anastomotic height (cm)	Bowels opened (day)	Diarrhoea occurred (day)	Abdominal pain (day)	Insidious bacteraemic shock	Delay to laparotomy (h)	Outcome
1	M	63	B	6	3	4	4	No	<1	Alive
2	F	62	C	3	7	10	12	Yes	36	Dead
3	M	78	C	3	10	25	25	Yes	12	Dead
4	M	53	B	4	5	6	6	Yes	5	Alive
5	M	64	A	5	4	5	5	Yes	8	Alive

Non-defunctioned group (n = 75)

In this group 50 patients had an anastomosis at 6 cm or lower and 25 had an anastomosis that was higher than 6 cm and less than 12 cm. Overall the mean(s.d.) anastomotic height was 6·0(2·0) cm. The mean anastomotic height for the entire group was significantly greater than for the defunctioned group ($P<0\cdot05$).

Although the exact incidence of anastomotic leakage is unknown in this group, 11 (15 per cent) patients developed symptoms which could be attributed to anastomotic leakage. In all 11 the anastomoses were end-to-end and were 6 cm or less from the anal verge.

In two of these patients no active intervention was necessary and their symptoms settled spontaneously. A further three patients required construction of a proximal colostomy; in two anastomotic disruption was found to be due to colonic ischaemia and in one patient a plastic drain was found to have eroded through the anastomosis. Of these three patients, two developed a rectovaginal fistula.

Six (8 per cent) of the patients who did not have a defunctioning stoma developed faecal peritonitis due to anastomotic failure and three of these patients had undergone non-curative resection due to extensive local disease. Comparison of the defunctioned and non-defunctioned groups of patients revealed that occurrence of faecal peritonitis was significantly greater in the patients who had not been defunctioned ($P<0\cdot01$). One of the six patients with peritonitis died from overwhelming sepsis before a laparotomy could be performed. The remaining five patients underwent a second laparotomy which confirmed the faecal peritonitis. Peritoneal toilet was performed, a defunctioning stoma was raised, and a distal colonic washout was carried out. The clinical features of these patients are given in *Table 1*. In each patient the blood supply of the colon appeared satisfactory. The anastomoses did not show evidence of gross disruption at reoperation except that leakage had occurred through a small defect producing general faecal peritonitis. It was not obvious in any of these cases that a retrorectal collection of blood or pus was the underlying cause of leakage from the anastomosis. In each patient convalescence had been smooth in the early days after operation. Each patient was initially thought to be progressing satisfactorily and each had an apparently normal bowel action. During subsequent days an attack of diarrhoea was followed by mild lower abdominal pain and insidious bacteraemic shock with minimal physical signs. This occurred between the fourth and 25th day after operation (*Table 1*). The time from onset of pain to the second laparotomy varied from 3 to 36 h. Three patients with a delay of less than 8 h recovered completely and later had their stomas closed after radiological confirmation of an intact anastomosis. The two patients in whom there was a delay of 12 h or more died.

Discussion

It is increasingly considered that a defunctioning colostomy may be safely dispensed with in low anterior resection[3,4]. This is of benefit to the majority of patients who recover, but the absence of a protective stoma still creates a potentially hazardous situation.

A low local recurrence rate is attributable mainly to total mesorectal excision and, to a lesser extent, the careful exclusion of exfoliated malignant cells from the operative field[1,2,6]. Total mesorectal excision does, however, leave behind a large fixed cavity in the pelvis in which a haematoma or abscess may form. Furthermore, after total mesorectal excision even an anastomosis as low as 3 cm from the anal verge is effectively intraperitoneal. Much of the pain-sensitive peritoneum is removed from the posterior pelvis so that the development of bacteraemic shock may be insidious Spreading peritonitis is all too easily missed after operation and anastomotic leakage should be considered in any case of unexplained deterioration. In the patients without a defunctioning stoma in the present study who developed leakage, anastomotic healing and postoperative recovery were both apparently proceeding normally, but peritonitis with minimal early symptoms and signs occurred in five patients.

In conventional and in higher anterior resections there is probably sufficient distensible rectum below the anastomosis to accommodate the arrival of a faecal bolus. Furthermore, the normal rectoanal inhibitory reflex still exists and may allow anal relaxation and escape of faeces Many surgeons provide a 'safety valve' by stretching the anal sphincter, but we have avoided this because of concern about long-term incontinence and soiling. In the low anterior resection described in this series there is virtually no rectum to accommodate the contents of a peristaltic wave. The normal rectoanal inhibitory reflex may be absent in the early postoperative period and descending faeces might impinge on a tightly closed sphincter. Consequently, the anastomosis could be placed under stress by the progressive collection of faeces which may then escape through any areas of weakness in the anastomotic ring.

It is interesting that an attack of diarrhoea occurred in five out of six patients at the time the patient became unwell Although it is not possible to determine whether an episode of diarrhoea was the cause or the effect of the anastomotic disruption, it is reasonable to speculate that intense peristaltic activity above a closed sphincter in combination with liquid stool provides the ideal circumstance for anastomotic leakage It is precisely this set of circumstances which is prevented by defunctioning

In this study, the patients who did not have a defunctioning stoma were those who were considered to be at minimal risk of anastomotic leakage. Despite this, peritonitis occurred in 8 per cent, ten times more often than in the defunctioned group. Thus it appears to be impossible to predict which patients are suitable for a single-stage procedure The single case of peritonitis in the defunctioned group shows the need to lavage the colon distal to a defunctioning stoma; proper defunctioning must include such a washout if bowel preparation is less than perfect

The consequences of leakage are much more serious when a colostomy has not been fashioned. Nearly half of the patients who developed peritonitis and septicaemia as a result of anastomotic leakage died, and anastomotic leakage caused almost half of the overall perioperative mortality rate in the series (1·5 per cent of a total 3·5 per cent) including the only death after curative resection in a patient under 70 years of age. Since no mortality or life-threatening morbidity could be attributed in the present series to the construction or closure of a transverse loop colostomy, such a colostomy may be regarded as a sensible precaution when sphincter conservation and wide total mesorectal excision have been undertaken, and when a stapled anastomosis is constructed at 6 cm or less from the anal verge.

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Comparison of restorative proctocolectomy with and without covering ileostomy in ulcerative colitis

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The experience of restorative proctocolectomy for ulcerative colitis is reported in 16 consecutive patients with no covering ileostomy (group 2) in comparison with 15 patients with a covering stoma (group 1); in each group a J pouch was constructed. All patients had pre- and postoperative clinical and manometric evaluations of the functional result up to 12 months. There were no deaths or permanent failures. The number of early complications was four in each group. Re-ileostomy was needed in one patient of group 1, and an ileostomy was constructed in three patients of group 2. At 1 year after operation the functional results did not differ between groups 1 and 2 in terms of daily frequency of defaecation (mean 5·6 and 5·4 in 24 h respectively), or in terms of anal basal or maximal squeeze pressures. There was a significant ($P < 0{\cdot}01$) *saving in total hospital stay (median 11 days) and in operating theatre time (mean 41 min) in patients with no covering ileostomy. It is concluded that a covering ileostomy may be unnecessary in restorative proctocolectomy, at least in suitable cases with no technical difficulty at the time of operation.*

Restorative proctocolectomy with ileal reservoir has become the first choice operation for most patients with ulcerative colitis[1–3]. Debate still continues about the best operative technique. For example, opinions vary about pouch design[2,4,5] and the method and optimal level of the pouch–anal anastomosis[6,7]. This reflects personal preferences in the hope of finding the safest and easiest method giving the best functional result.

Another controversial issue is the necessity of a defunctioning ileostomy. It was regularly used when this demanding operation was first introduced[1,3], but with increasing experience some groups have abandoned it[4,8–10] with no hazardous consequences.

Covering ileostomy was omitted as a routine in this department in May 1988 after an experience of 48 restorative proctocolectomy operations, and since then a covering stoma has been considered necessary in only two (4 per cent) of 52 cases because of technical difficulty. The follow-up results of the first 16 patients without covering ileostomy are reported here and compared with the 15 previous patients with ileostomy.

Patients and methods

Patients

Between November 1987 and April 1988 15 patients with ulcerative colitis underwent restorative proctocolectomy with a covering ileostomy (group 1). The ileostomies were closed 2–4 months later (mean 2·4 months) in all cases. Group 2 consisted of 16 patients with ulcerative colitis operated on between May 1988 and February 1989 without covering ileostomy. The basic patient data of these two consecutive groups did not differ significantly (*Table 1*).

Methods

The operative technique was identical throughout the study period except for the incorporation or otherwise of the ileostomy. After conventional colectomy, saving the omentum and excising the rectum as far distally as possible, a J pouch with 15–20-cm limbs was constructed using the GIA 90 and 45 staplers (US Surgical Corporation and Autosuture UK, Ascot, UK). The stapler opening in the upper part of the pouch was hand sewn in two layers of continuous 3/0 polyglyconate sutures. A complete mucosectomy was performed peranally, and the pouch–anal anastomosis was hand sewn using 3/0 polyglyconate. A 28 Fr gauge silicone catheter (Medena, Astra Meditec, Mölndal, Sweden) was used to drain the pouch for 5 days. In patients of group 1 a loop ileostomy was constructed as distally as possible, and the loop was rotated through 180° to position the proximal bowel opening inferiorly.

Anal manometry and clinical functional assessment were performed before the operation, before ileostomy closure (group 1), and at 3, 6 and 12 months after operation. Manometry was performed using an open 8 Fr gauge perfused polyvinyl catheter and the continuous pull-through method[11].

Statistical analysis between the groups was performed using the two-tailed Mann–Whitney *U* test.

Results

There were no deaths or permanent failures. Four patients in each group had early complications after operation (*Table 2*). In group 1, two patients had to be reoperated on. In group 2 one patient developed peritonitis 1 week after the operation caused by faecal leak from the suture line in the upper pouch; this was closed and an ileostomy fashioned and kept for 6 weeks. Other early complications were managed conservatively.

Table 1 *Description of patients in the study groups*

	Group 1 Covering ileostomy ($n=15$)	Group 2 No ileostomy ($n=16$)
Age in years	36·6	31·6
S.d.	9·7	9·9
Range in years	20–53	18–51
No. of men	10	7
No. with previous colectomy with ileostomy	5	2

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Table 2 *Complications after operation*

No. of complications	Group 1 Covering ileostomy ($n=15$)	Group 2 No ileostomy ($n=16$)
Early		
Haemorrhage	3*	1
Septicaemia	–	1
Pouch perforation	–	1*
Leg compartment syndrome	1*	–
Urine retention	–	1
Late (>1 month)		
Bowel obstruction	2*	2*
Anastomotic sinus	1†	3†
Pouchitis	3	1
Peritonitis (after ileostomy closure)	–	1†

* One reoperation following complications. † Two reoperations following complications

Table 3 *Functional results at 12 months after surgery*

	Group 1 Covering ileostomy ($n=15$)	Group 2 No ileostomy ($n=16$)
Defaecation		
Frequency per 24 h	5·6	5·4
S.d.	2·3	2·1
Range	2–12	2–10
No. with night evacuations	4	5
No. with daytime soiling	2	0
No. with nighttime soiling	4	2
No. wearing a pad	4	1
No. using antidiarrhoeal medication	2	2
No. pensioned after surgery	1	1

Late complications occurred in six patients in each group (*Table 2*). One patient of group 1 had bowel obstruction and abscess at the ileostomy closure site from suture line leak; this was sutured and drained. One patient later developed anastomotic sinus and needed a re-ileostomy which was subsequently closed. In group 2, three patients had anastomotic sinuses one of which healed with antibiotics. In two others a covering ileostomy was needed; and although these were later closed this resulted in suture line leakage and peritonitis in one case. After two reoperations including re-ileostomy, the stoma was closed 1 year after the primary operation. One further patient in each group had bowel obstruction treated conservatively, and one patient in group 2 had to be operated on because of pouch obstruction.

At 1 year after the primary operation all patients had a functioning ileoanal anastomosis. The function was graded as good (26 patients) or moderate (five patients) with no significant difference between the groups (*Table 3*). The groups did not differ in anal pressure recordings at any time after the operation (*Figure 1*).

The total hospital stay (median 26 compared with 15 days) and time of health insurance payment (median 105 compared with 84 days) are shown in *Figure 2*. The saving of 11 hospital days was significant ($P<0{\cdot}01$) in patients without ileostomy, and they also had 21 days less sick-leave ($P>0{\cdot}05$). The mean operation time was 274 min in group 1 (range 210–455 min) and 233 min in group 2 (range 170–295 min); i.e. 41 min less in those without covering ileostomy. As closure of the ileostomy took a mean of 32 min, there was a significant saving of operating theatre time in group 2 ($P<0{\cdot}01$).

Discussion

The increasing number of patients undergoing restorative proctocolectomy made it sensible to search for the most effective way of managing these time consuming procedures. Difficulty in finding scheduled operating times for stoma closure was one reason for us to question the necessity of a covering ileostomy. The present comparison of two consecutive groups of patients showed no significant increase in complications after operation

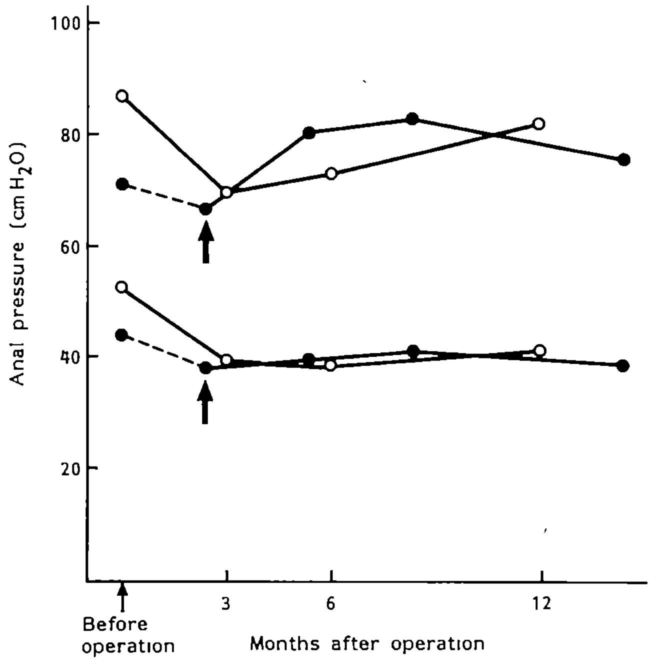

Figure 1 *Maximal (upper) and basal (lower) anal squeeze pressures in group 1 (●) and group 2 (○) after restorative proctocolectomy. Arrow indicates ileostomy closure time in group 1. Differences between the groups were not significant*

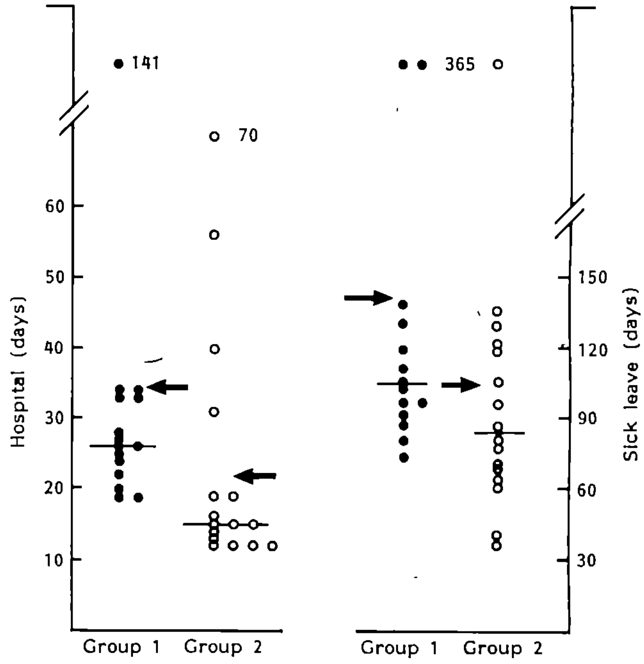

Figure 2 *Length of total hospital stay (left side) and of health insurance payment (right side). Arrows indicate means (34·1 compared with 21·5 days, and 141 compared with 104 days in groups 1 and 2, respectively) and bars indicate medians (26 compared with 15 days, and 105 compared with 84 days, respectively). Hospital stay was significantly less (median 11 days, P<0·01) in patients without ileostomy (group 2)*

and no sign of compromise of functional outcome in those without ileostomy. There were no permanent failures in either group, and the number of patients with a good functional result compares favourably with reports from other centres[12–14]. Thus, it seems reasonable to state that savings in operating theatre time and hospital stay were not achieved at the expense of a high risk of failure of poor functional reult.

The present comparison may be criticized because the patients with ileostomy were operated on earlier, and increased experience might have influenced the latter group favourably. However, the operative technique was already familiar to us from 32 previous restorative proctocolectomies since 1985. We also found it very difficult to give patients good reason for a randomized study about this particular issue.

Even if avoidance of a covering ileostomy is economically justified and causes no increase in complications, there remains the risk that a covering ileostomy must be constructed later if an anastomotic leak occurs. This happened in three of the present patients, and has been noted in about 10 per cent in other small series without ileostomy[8,9,15]. On the other hand, anastomotic sinuses or other complications may necessitate a re-ileostomy even after successful closure of the ileostomy, as happened to one of our patients. A further two of 18 patients had a leak at the ileostomy closure site, indicating that the closure of the stoma is not a totally harmless procedure. In other series 3 and 7·4 per cent of patients developed peritonitis after the closure[14,16]. Matikainen *et al.*[17] had stomal problems in half of their patients, while only one of 25 without ileostomy needed a stoma later So, the complications and harm of covering ileostomy may be as great as those of its avoidance.

Our further experience in restorative proctocolectomy without ileostomy has resulted in decrease in the need for later stomas to six of 50 patients. Peck has used stapling for the pouch-anal anastomosis with no need for later stomas[10]. The stapler technique also seems to preserve better continence if 1 or 2 cm of the transitional mucosa above the dentate line is left behind[18,19]

On the other hand, preserving of any rectal mucosa involves the risk of residual proctitis and even a small cancer risk. In addition, internal sphincter damage may still result although mucosectomy and anal retractions are omitted in the stapled anastomosis[7]. In the present study anal basal pressures decreased less (13–25 per cent) than was observed in our previous experience (45 per cent)[11]. This was the result of better technique with less retraction during mucosectomy which was performed in a shorter time.

Pelvic sepsis is a major factor influencing the functional outcome, and it is closely related to the experience of the surgeon[13]. Therefore, adequate experience with the technique of restorative proctocolectomy is important before omitting covering ileostomy. In cases with technical problems such as tension at the anastomosis, a covering stoma still is the safer option. The best technique for performing the pouch-anal anastomosis in cases without ileostomy remains to be established by randomized trials, e.g. comparing stapling with hand suture.

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Principal causes of mechanical bowel obstruction in surgically treated adults in Western Turkey

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A retrospective study of the principal causes of mechanical bowel obstruction occurring in Western Turkey between 1979 and 1989 was undertaken. The records of 14 777 operations performed in the general surgery departments of two hospitals were reviewed. Mechanical bowel obstruction occurred in 582 patients. Among the causes of mechanical bowel obstruction, adhesions were most common (44·0 per cent), followed by strangulated hernia (23·9 per cent), volvuli (12·7 per cent) and colonic carcinomas (10·1 per cent). A previous appendicectomy appeared to be the most important cause of adhesions causing mechanical bowel obstruction.

Causes of mechanical bowel obstruction seem to vary from one country to another and the incidence of the various aetiological factors appears to alter from year to year. The present study was carried out to investigate the principal causes of mechanical bowel obstruction in Western Turkey, and to compare these with those encountered in other countries. With this in view, a study was undertaken in two major hospitals in İzmir, a large city and an important health centre in Western Turkey.

Patients and methods

The records of 14 777 cases were reviewed. All patients had been operated on by the authors in the general surgery departments of the two hospitals within the decade January 1979 to January 1989. A retrospective study was carried out on 582 cases operated on for mechanical bowel obstruction, with particular reference to aetiology, age and sex distribution. The notes were obtained for all patients admitted with a presumptive diagnosis of mechanical bowel obstruction. In addition, the operating theatre register was reviewed and cases diagnosed during operation as mechanical bowel obstruction were identified. Cases diagnosed as paralytic ileus and those cases of obstruction treated by non-surgical methods were excluded from the study

Results

An evaluation of 582 cases of mechanical bowel obstruction from the standpoint of aetiology, age and sex distribution, is presented

Aetiology

Adhesions were found to be the aetiological factor in 256 cases (44·0 per cent), strangulated hernia in 139 (23·9 per cent), colonic volvulus in 74 (12·7 per cent), malignant tumour of the colon in 59 (10·1 per cent), intussusception in 10 (1·7 per cent), and other causes in 44 (7·6 per cent). The distribution of 582 patients on the basis of aetiology is outlined in *Table 1*.

Of 256 cases of adhesion 98 (38·3 per cent) had a previous history of appendicectomy, six had a history of tuberculosis, no particular cause was determined in four, while the remaining 148 cases had undergone various abdominal operations. The previously performed operations on the adhesion group are presented in *Table 2*. Of 139 cases of strangulated hernia, 72 had inguinal, 41 femoral, 14 incisional, and 12 other types of hernia. Of 74 cases of colonic volvulus, 71 were of the sigmoid colon and three of the caecum. Of 59 cases of colonic tumour, 50 were located at the left colon and nine at the right colon. Of the 10 cases of intussusception four were due to lymphoma, three to metastatic tumours and two to Meckel's diverticulum. In one case the aetiological factor could not be determined. Only in one of these cases was there invagination of the ileocaecal type due to a metastatic tumour, all of the rest being at the level of the small intestine.

Age distribution

As the study was conducted in adult clinics all the subjects were

Table 1 *Cause of obstruction in 582 patients*

Adhesions ($n=256$)	
Previous operations	246
Tuberculosis	6
Cause not found	4
External hernias ($n=139$)	
Inguinal	72
Femoral	41
Postoperative	14
Others	12
Volvulus ($n=74$)	
Sigmoid	71
Caecum	3
Colonic tumour ($n=59$)	
Caecum	3
Ascending colon	2
Hepatic flexure	5
Splenic flexure	7
Descending colon	10
Sigmoid colon	16
Rectosigmoid junction	12
Rectum	4
Intussusception ($n=10$)	
Lymphoma	4
Metastatic tumour	3
Meckel's diverticulum	2
Cause not found	1
Others ($n=44$)	
Bezoar	8
Gallstone ileus	7
Ogilvie's syndrome	7
Worms	5
Radiation stricture	3
Internal hernia	4
Diverticulitis	3
Regional enteritis	2
Chronic ulcerative colitis	2
Extrinsic masses	2
Faecal impaction	1

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Table 2 *Previous operation in adhesive obstruction* ($n=246$)

Previous operations	*n*
Appendicectomy	98
Hysterectomy	28
Partial gastrectomy	23
Colon resection	19
Surgery for penetrating abdominal trauma	18
Cholecystectomy	17
Surgery for ruptured ectopic pregnancy	15
Miscellaneous	28

over the age of 15 years. The ages ranged from 16 to 94 years with a mean of 56·8 years.

Sex distribution

Of the 582 patients, 194 were women and 388 were men; the female:male ratio was therefore 1·2.

Discussion

In recent years, the aetiological aspect of bowel obstruction has been subject to considerable changes. The progressively increasing number of abdominal operations performed and early operation of inguinal hernias before strangulation seem to account for these changes[1]. In a retrospective study conducted in the UK, strangulated hernias were found to have accounted for 50 per cent of all the cases of bowel obstruction between 1925 and 1930, malignancy for 23 per cent, and adhesions for 7 per cent[2]. However, various investigations carried out during the past two decades have shown that the spectrum of bowel obstructions in the UK has been considerably altered[3,4]. In these studies, adhesions were the most common aetiological factor followed by colorectal cancer and strangulated hernias. Similar changes were observed in studies conducted in the USA. In a study covering the period 1942–1945, in contrast to the previous findings, adhesions were found to account for 31 per cent of the cases of mechanical bowel obstruction, malignancies for 27 per cent, and strangulated hernias for 10 per cent[5].

The figures obtained in Turkey seem to agree with these findings, although the change in aetiological factors has occurred 20–30 years later than in Western societies. The statistics covering the period 1963–1973 in one of the hospitals in this study showed strangulated hernias to rank first at a rate of 55·6 per cent, whereas in the present report covering the last 10 years adhesions occupy the first position (44·0 per cent) followed by strangulated hernias (23·9 per cent), volvulus (12·7 per cent) and colonic tumour (10·1 per cent). Although the order recently observed in Turkey seems to be similar to that reported in Western societies, the frequency of volvuli constitutes a disparity. Cases of sigmoidal volvulus are reported to be quite common in some African and Asian societies[6] We are inclined to attribute the frequency of the cases of volvulus in Turkey to the high consumption of dry chickpeas and beans which are sources of intestinal gases.

An investigation of the age distribution of the patients suffering mechanical bowel obstruction does not yield a significant difference among the groups. However, the patients in the group with volvulus and colonic tumour appear to be older. Yet, due to the fact that the average life span in Turkey is shorter than that in Western societies, the frequency of the cases of volvulus and colonic malignancy which occur in the seventh and eighth decades of life in Western societies is observed to occur in the fifth and sixth decades of life in the present series.

Turkey is a rapidly developing country and, as in Western society, the causes of bowel obstruction have changed Obstruction due to adhesions is now the commonest cause and probably relates to the increasing rate of surgical intervention Volvulus, which is rarely encountered in the West, still ranks third among the causative factors and may relate to dietary factors.

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Reoperations for late complications following abdominal aortic operation

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Fifty patients were identified who, following abdominal aortic operation, developed late complications affecting the vascular graft or endarterectomy and who underwent their first reoperation between 1979 and 1989. Thrombosis was the commonest complication affecting 28 (56 per cent) patients, followed by false aneurysm in 11 (22 per cent), enteric fistula in nine (18 per cent) and graft infection in two (4 per cent). The 30-day mortality rate for reoperation was 8 per cent; longer follow-up revealed mortality rates of 22, 50 and 63 per cent at 1, 3 and 5 years respectively. Thirty-four complications required reoperation within 5 years of the original surgery. Reoperation was needed for 35 patients whose original pathology was occlusive disease and for 15 whose original pathology was aneurysm. The nature of the complication was related to initial pathology; thrombosis was far commoner in those with occlusive disease, and enteric fistula and false aneurysm were commoner in those with aneurysmal disease.

Aortoiliac reconstruction is regarded as having a relatively low incidence of complications compared with peripheral reconstruction. Five-year patency rates of about 85 per cent for aortoiliofemoral reconstruction imply a thrombosis rate of 15 per cent in the first 5 years after operation[1–3]. There is a continuing steady attrition of grafts over subsequent years[4]. Other late complications occurring after discharge from hospital include false aneurysm, infection, enteric erosion and graft–enteric fistula[5]. The last two may present as infection or gastrointestinal haemorrhage. Survival rates of 43 per cent at 10 years and 30 per cent at 15 years have been reported after aortofemoral bypass for occlusive disease and so there is a large number of patients at risk of such late complications[6]. It is evident that, as the number of aortic operations increases, so will the number of complications and revisional procedures[7]. This is a report of 50 consecutive patients who had aortic surgery and who required reoperation in this unit for late complications between 1979 and 1989, a period of 11 years.

Patients and methods

Using the Lothian Surgical Audit, patients were identified who had had aortic grafts or aortoiliac endarterectomy for occlusive or aneurysmal disease, and who thereafter underwent revisional surgery for a late complication of the original operation[8] To ensure that all patients were included, these data were checked against operations registers Fifty patients were identified. There were 39 men and 11 women of mean(s.d.) age 57(9) years (range 39–76 years) In 35 patients the original pathology was occlusive arterial disease, causing claudication in 24 and ischaemic rest pain and/or gangrene in 11. The remaining 15 patients had aneurysmal disease, asymptomatic in two, symptomatic in five and ruptured in eight. Thirty-nine of the original operations had been performed by consultants, seven by senior registrars under consultant supervision, and four by senior registrars alone

Between the years 1976–1989 (a period starting 3 years before the first reoperation) 709 patients had aortic grafts for aneurysmal disease and 393 for occlusive disease. However, because some of the 50 patients had their original operation outside this region and further patients may still develop late complications requiring reoperation, the incidence of these late complications cannot be accurately assessed. We know of no cases where patients have had reoperation at other centres after a primary operation at this centre, and think it unlikely because Edinburgh is the tertiary referral unit for the region and few patients of this age group move to another region.

The nature of the complication, its treatment and the outcome were obtained from case records. Also noted were patients who had amputation following reoperation and those who had further revisional surgery as a consequence of complications of the reoperation. If the most recent case record entry was more than 4 months old, the present condition of the patient was obtained from the general practitioner if he or she had seen the patient within the last 4 months If this was not the case, the patient was contacted directly. In this way up-to-date records were obtained for 49 of the 50 patients. One patient was untraceable for the past year and in this case data at the last available follow-up (65 months after reoperation) were used Data are in general presented as mean(s d) with the range where appropriate. Groups of patients were compared using the χ^2 test with Yates' correction

Results

The nature of the original surgery is shown in *Table 1* Eight patients had had their original operation in another hospital outside the region. This paper deals with late complications, i.e. those occurring after discharge from hospital. The mean interval between the original operation and reoperation was 50 months with a range of 2–220 months (*Figure 1*). Thirty-three patients (66 per cent) underwent reoperation within 5 years of the initial operation. The primary pathology, original operation and complication leading to reoperation are shown in *Table 2.*

The commonest complication requiring reoperation was thrombosis, occurring in 28 (56 per cent) of the 50 patients. This problem was encountered in 27 (77 per cent) of the 35 patients with occlusive disease and in only one of the 15 patients with aneurysmal disease ($P < 0{\cdot}001$). On the other hand, both enteric fistula and false aneurysm were commoner in patients whose original operation had been for aneurysm. Of the 35 patients with occlusive disease three (9 per cent) had fistulae and four (11 per cent) had false aneurysm, while of the 15 whose original surgery was for aneurysm six (40 per cent) had fistulae ($P > 0{\cdot}05$) and seven (47 per cent) had false aneurysm ($P < 0{\cdot}05$).

Thrombosis

Thromobosis occurred after aortoiliac endarterectomy in five patients. At reoperation four had an aortobifemoral graft and one had an axillobifemoral graft. The mean(s.d.) interval between initial surgery and reoperation was 133(55) months. Three patients required a total of six further revisional vascular operations. Three patients are alive after a mean follow-up time

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Table 1 *Pathology and original operation in 50 patients*

Original operation	Pathology Occlusive (*n*=35)	 Aneurysmal (*n*=15)
Endarterectomy	6	0
Tube graft	0	5
Aortobi-iliac graft	6	7
Aortobifemoral graft	18	3
Aortoiliac/femoral graft	3	0
Aortounifemoral graft	2	0

Table 2 *Primary pathology, original operation and complication leading to second operation*

Operation (pathology)	Complication Thrombosis	 False aneurysm	 Infection	 Enteric fistula
Endarterectomy (occlusive)	5			1
Tube graft (aneurysm)		2		3
Aortobi-iliac graft (occlusive)	4	1		1
Aortobi-iliac graft (aneurysm)	1	3		3
Aortobifemoral graft (occlusive)	13	3	1	1
Aortobifemoral graft (aneurysm)		2	1	
Aortoilio/femoral graft (occlusive)	3			
Aortounifemoral graft (occlusive)	2			

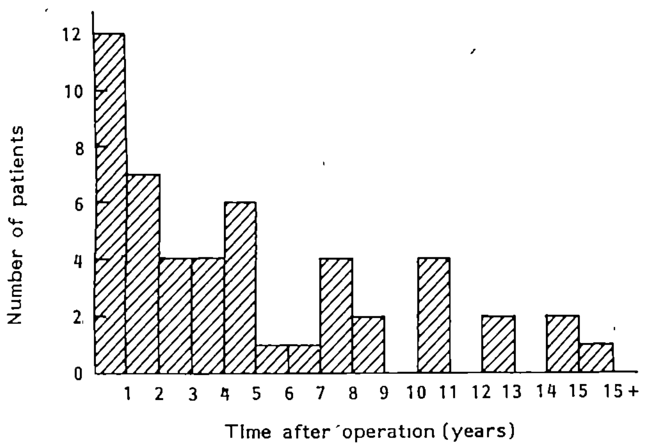

Figure 1 *Interval from original operation to reoperation in 50 patients*

of 66 months and two have died, at 56 and 98 months respectively after reoperation, one of whom had an amputation

Graft thrombosis occurred in 23 patients This was corrected by graft thrombectomy in four cases. Thrombectomy or replacement of an occluded graft limb combined with a procedure to improve outflow was required in 12 patients (extension of graft to profunda femoris, adding a graft-to-popliteal extension, extending iliac limbs to the femorals, etc.). A further four patients had complete graft replacement with or without extension of distal anastomoses, and a cross-over procedure was used in the final three cases The mean(s.d.) interval between original operation and reoperations was 40(44) months. Eleven patients required a total of 18 further revisional operations. Thirteen patients are alive after a mean follow-up time of 32 months; two of these patients have required amputation. Ten patients have died at a mean of 27 months after reoperation. Five of these had an amputation before death.

False aneurysm

False aneurysm occurred in 11 patients. This affected the proximal (aortic) anastomosis of two bifurcated grafts and the distal anastomosis of two aortic tube grafts. The remainder occurred at iliac or femoral anastomoses. They were dealt with either by replacement of the entire graft with extension beyond the site of the false aneurysm (five cases) or by partial graft resection and extension beyond the aneurysm (six cases). The mean(s.d.) interval between original operation and reoperation was 81(51) months and three patients have required a total of eight further revisional vascular operations. Three of these were for false aneurysm developing on the contralateral side (one iliac and two femoral). Nine patients are alive after a mean follow-up period of 33 months. One has required amputation. Two patients died at 15 and 23 months respectively following reoperation.

Graft infection (without enteric fistula)

There were two patients with infection without fistula. Both infections were in the groin and were dealt with by excision of the involved graft limb and its replacement with another graft rerouted away from the infected field. The intervals between primary operation and reoperation were 2 and 3 months respectively. Neither patient required further revisional surgery. One patient is alive 84 months after reoperation; the other died from overwhelming sepsis 2 weeks after reoperation.

Enteric fistula

There were nine patients with fistulae. One followed aortoiliac endarterectomy and was treated by excision of the iliac artery, which was replaced with a Dacron® (E.I. du Pont de Nemours and Company, Wilmington, USA) graft. This patient is alive after a follow-up period of 17 months. The remaining eight patients had graft–enteric fistulae Three presented with signs of sepsis and five with gastrointestinal bleeding. Second operations included graft excision and axillobifemoral bypass (three cases), replacement of all (three cases) or part of the graft (one case) and simple removal of the graft with no reconstruction (one case). The mean(s.d.) interval between original operation and reoperation was 38(39) months and three patients required a total of nine further revisional procedures. Two patients are alive after 17 and 77 months respectively. One had an axillofemoral bypass and tube graft removal, followed by unilateral amputation The other had removal of an aortobifemoral graft and replacement with a new aortobifemoral graft. Six patients died, at a mean of 14 months after reoperation.

In summary, of the total group of 50 patients, 21 have died. Follow-up of the 29 patients still living ranged from 3 to 108 months with a mean(s.d.) of 38(33) months Patients who died did so within 0–98 months after reoperation with a mean(s.d.) time to death of 26(30) months. Of those who died, nine had further operations to correct further problems with the graft and eight required above-knee amputation before death. Of the patients alive, ten required further surgery for graft complications and four had above-knee amputation.

Twenty-seven patients have been followed up for at least 5 years or died within 5 years of reoperation. At a follow-up period of 5 years, 17 patients were dead and seven had had above-knee amputation before death Of the ten survivors, two had had above-knee amputations. The mortality rate for reoperation was 8 per cent within 30 days, and 22, 50 and 63 per cent at 1, 3 and 5 years respectively.

Discussion

Not surprisingly, graft thrombosis was the commonest complication and it was generally held to be due to progression of distal disease. The reported incidence of concurrent aortoiliac and femoropopliteal disease is between 45 and 65 per cent[9–13]. Re-establishing graft patency was, in the majority of cases, accompanied by a procedure to improve run-off, a manoeuvre that has been shown to increase the patency rate following thrombectomy[14]. The decision to reoperate for thrombosis is often complex and depends on limb viability, the condition of the patient, and the pathology that led to thrombosis. Because the original operation was justified does not mean that a second operation is, but most patients with occlusions following aortoiliac reconstruction will present with critical ischaemia[4].

Thirty-five (70 per cent) of the reoperations were required when the primary pathology had been occlusive disease, despite the fact that over the 14-year period only 36 per cent of primary operations were for occlusive disease. Occlusive disease appears to carry a four times greater risk of reoperation than aneurysmal disease.

It is interesting that the late complications which affected patients whose initial operation had been for aneurysm differed so profoundly from those seen after surgery for occlusive disease. Graft thrombosis was a rare event, affecting only a single patient who had aneurysm surgery. This corroborates the impression that aortoiliac aneurysm is less often associated with distal occlusive disease than is aortoiliac occlusive disease. On the other hand, reconstructions for dilating disease were associated with later false aneurysm formation and enteric fistula. The graft and, especially, vascular suture lines within the abdomen should be carefully covered at the end of the operation with aneurysm sac or, if this is not possible, with omentum. Prophylactic antibiotics should always be used and, especially in the groin, a tense, overstretched graft should be avoided and as generous an amount of arterial wall as possible should be incorporated in the suture line[15].

Whether better run-off or better suture line coverage could have been effected for any or all of the patients discussed in this series cannot be assessed. What is certain, however, is that the outlook for those who develop late complications is poor. Not only is the perioperative (30-day) mortality rate high (8 per cent), but the 5-year survival rate is only 37 per cent.

In conclusion, vascular surgeons should be aware that the outcome after revisional surgery for late aortic complications is poor and, therefore, every precaution must be taken at the time of original surgery. Particular attention should be paid to maximizing run-off in those with occlusive disease and to care of the vascular suture line in those with aneurysm.

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Light reflection rheography: an effective non-invasive technique for screening patients with suspected deep venous thrombosis

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Light reflection rheography is a simple non-invasive technique for assessing venous function in the leg. One hundred and twenty-four patients referred for venography with a clinically suspected deep venous thrombosis were investigated by light reflection rheography to determine the accuracy of the technique in diagnosing acute thrombosis. In half of the patients venography confirmed a deep venous thrombosis. Light reflection rheography had a sensitivity of 92 per cent and a specificity of 84 per cent in detecting acute thrombosis. The technique had a negative predictive value of 92 per cent in selecting those patients with no thrombosis. Light reflection rheography can be performed at the bedside or in the radiography department which makes it a suitable technique for screening patients with suspected deep venous thrombosis.

Deep venous thrombosis in the lower limb is a common condition with potentially lethal complications. It is often difficult to make the diagnosis because two-thirds of patients remain symptom-free[1]. Even clinicians with specialist experience in treating these patients report a high rate of clinical diagnostic error[2]. Non-invasive tests such as ultrasonography and plethysmography improve the accuracy[3], but many physicians still diagnose and treat deep venous thrombosis solely after clinical observation[4]. The reluctance to use non-invasive tests may be due to the difficulty in performing such tests, particularly out of hours. Nevertheless a reliable technique for confirming the diagnosis is required if the unnecessary treatment of clinically misdiagnosed deep venous thrombosis is to be avoided. Venography is readily available and is the only technique that gives information on the extent of the disease[5], but it is invasive and carries a significant morbidity rate. Furthermore since half the patients suspected clinically of having a deep venous thrombosis will have a normal venogram, venography is an expensive method of screening such patients.

Light reflection rheography is a new technique based on the principle of photoplethysmography[6] but incorporating three light-emitting diodes within the sensor head rather than a single electrode. The results of light reflection rheography have been shown to correlate with venous pressure changes[7] and the technique has been used in the assessment of patients with chronic venous insufficiency[8].

This study was undertaken to determine the accuracy of light reflection rheography in confirming thrombosis in patients with a clinical suspicion of deep venous thrombosis.

Patients and methods

The study was prospective and consecutive. All patients having venography for suspected deep venous thrombosis were included and, because they were referred by different clinicians, the clinical criteria for diagnosis were not standardized. In some patients bilateral venography was requested. Light reflection rheography was performed on both legs in all cases. The investigation was conducted independently of the referring clinician and the light reflection rheography results did not influence patient management. Light reflection rheography was performed by the vascular technician or registrar on the same day as the venography. Both investigations were reported independently of each other and without reference to the clinical notes. The results of light reflection rheography were compared with those of venography and the predictive value of the technique in diagnosing deep venous thrombosis was assessed.

Light reflection rheography

Light reflection rheography depends on the principle that light in the infrared range produced from three light-emitting diodes is absorbed by red cells in the dermal venous plexus. In normal subjects a reduction in venous pressure during exercise is associated with a decrease in the amount of blood in the venous plexus of the calf, a decrease in light absorption and a resultant increase in light reflectivity. The reflected light is detected by a central photodetector within a sensor head. During the rest period after exercise the dermal venous plexus gradually refills and light reflectivity returns to baseline values. In patients with venous thrombosis, venous obstruction prevents the emptying of the venous plexus so that no increase in reflectivity occurs (*Figure 1*).

The instrument (Haemodynamics AV1000, Zyma, Alderley Edge, Cheshire, UK) is portable and this permits evaluation of patients at the bedside or in the radiography department. Patients were asked to sit with their legs dependent and their feet on the floor for 5 min to allow complete filling of the calf veins and dermal plexus. The sensor head was attached to the calf approximately 10 cm above the medial malleolus and behind the tibia using double-sided adhesive tape. In a standardized test patients performed ten dorsiflexions of the foot in time to a metronome incorporated into the instrument, after which the foot was rested on the floor for a further 40 s.

The test was performed twice on each limb, and in patients with equivocal results or those with varicose veins it was repeated using a tourniquet and at higher sensitivity. The criteria for a positive result was a flat, or virtually flat, tracing indicating significant venous obstruction.

Venography

Venography was performed using a standard ascending technique[9]. Films were reviewed by two consultant radiologists without reference to the clinical notes. The level of the thrombosis was recorded and patients were separated into those with thrombus in the calf only and those in whom thrombus extended into the popliteal, femoral and iliac vein. The presence of collaterals was also recorded.

Results

One hundred and twenty-four consecutive patients with suspected deep venous thrombosis were referred for venography over a 5-month period. Venography was not performed in four patients (failed cannulation in three, early pregnancy in one) and the venograms and records of one patient were lost. In 12

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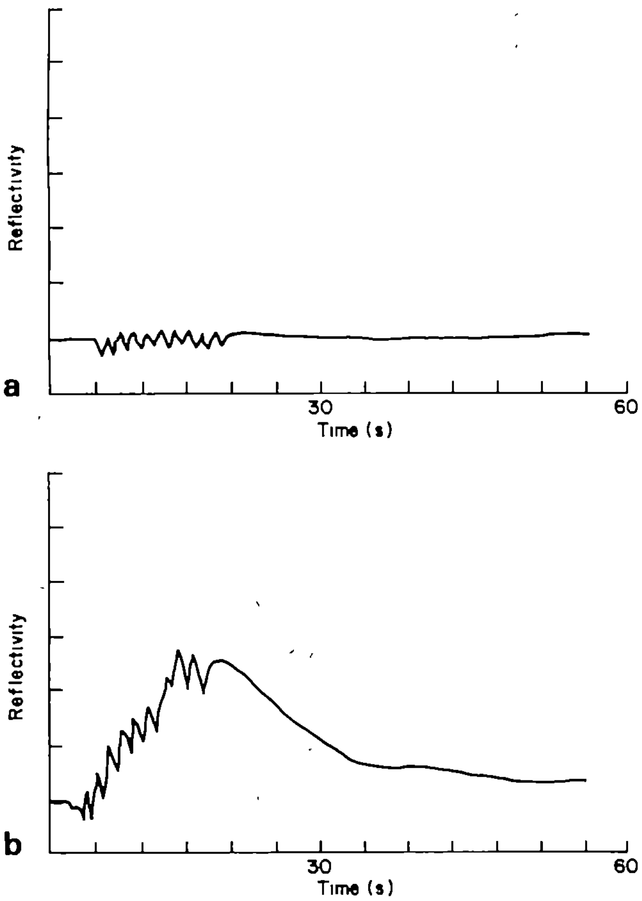

Figure 1 *Light reflection rheography results from a patient with deep venous thrombosis in the right leg confirmed on venography* **a** *right leg;* **b** *left leg*

patients bilateral venography was performed, eight of whom had presented with a suspected pulmonary embolus. Thus 131 legs in 119 patients were available for analysis. The patients, 52 men and 67 women of mean age 58 years, were referred from the following sources: medical outpatients 14, medical inpatients 80, postoperative surgical 25.

The findings on venography and the results of light reflection rheography are summarized in *Table 1*. A deep vein thrombosis was confirmed by venography in 61 of the 131 limbs giving a diagnostic accuracy of 47 per cent. Of these 61 deep vein thromboses, 56 were accurately predicted by light reflection rheography (sensitivity 92 per cent) whilst 59 of the 70 limbs without a thrombosis were identified (specificity 84 per cent). The positive predictive value of light reflection rheography was 84 per cent and the negative predictive value was 92 per cent.

Of the limbs with a deep venous thrombosis, 18 (30 per cent) had thrombus limited to the calf veins, 12 (20 per cent) had isolated thrombus in the proximal veins, and the remaining 31 (51 per cent) limbs had thrombus in both the calf and proximal vessels. The level of thrombosis did not affect the sensitivity of light reflection rheography (calf veins 94 per cent, proximal vessels 90 per cent, $P>0{\cdot}05$, χ^2 test).

Although venography was performed only in the suspect limb, both legs were assessed by light reflection rheography. In 15 per cent of patients the light reflection rheography tracing suggested the presence of a deep venous thrombosis in the asymptomatic limb.

Discussion

Acute venous thrombosis carries a significant morbidity, and pulmonary embolus is a potentially fatal complication. Clinicians have a high suspicion for thrombosis which leads to a high demand for contrast venography. It is recognized that over half of patients with symptoms suggestive of venous thrombosis will not have the condition even in the presence of calf pain and swelling[1,10]. In this study less than half of the venograms were positive and this confirms previous experience[2]. This high rate of negative venograms results in unnecessary morbidity[11].

Venography is recommended before treatment of deep venous thrombosis. The level, extent and age of the thrombus can be assessed and appropriate treatment given. Venography can sometimes be unreliable because it gives relatively poor imaging of the pelvic veins and vena cava, and small calf thrombi are not always visualized. Furthermore, the test cannot be repeated and gives information on only one limb. ^{125}I-labelled fibrinogen studies have shown that in as many as 40 per cent of patients thrombi are present in the contralateral limb[12]. In this study the light reflection rheography results suggested that as many as 15 per cent of patients may have had a significant thrombosis in the asymptomatic limb.

In ten patients (11 limbs) light reflection rheography predicted a deep venous thrombosis but venography subsequently proved negative. This group was significantly older (mean age 75 years, $P<0{\cdot}05$, χ^2 test) than the other patients and the patients had a variety of medical problems which interfered with the performance of the test. Three octogenarians had congestive cardiac failure and leg oedema which resulted in low reflectivity. Low reflectivity may also be due to vasoconstriction or peripheral vascular disease and does not produce a diagnostic trace. Four patients could not dorsiflex their ankles (two were bed-bound, one had a hemiplegia and one had a ruptured Achilles tendon) and were unable to perform the test properly. Of the other three patients one gave a history of previous deep venous thrombosis, in one there was uncertainty in the interpretation of the films and in one there was no explanation.

Five patients had a thrombosis which was not detected by light reflection rheography. On review of the tracings at the end of the study it was felt that one, in the light of further experience, should have been classified as positive. Two of the patients had been started on heparin before testing by light reflection rheography which might have affected the result. In the other two patients a partially obstructing thrombus was not detected and these represent true false negative results.

In some patients both legs were abnormal which made it difficult to decide whether the tracing should be classified as positive or negative. In such cases the tracing should be classified as abnormal; a small false positive rate is acceptable since light reflection rheography is a screening technique and all these patients should proceed to venography.

Plethysmographic techniques have been criticized for their low sensitivity in detecting non-occlusive thrombi especially when limited to the calf veins[5] In this study light reflection rheography showed no difference in sensitivity in detecting thrombus at different levels and was able to detect all but two non-occlusive thrombi. We feel this may be due to the effect of coexistent thrombus within the smaller vessels of the calf adjacent to the probe. In a study of more than 1000 patients with suspected deep venous thrombosis and normal impedance plethysmography, the incidence of suspected or proven pulmonary embolism was less than 1 per cent[13].

Table 1 *Comparison of the results of light reflection rheography and venography in 119 patients (131 limbs)*

	Light reflection rheography		
	Positive	Negative	Total
Venography			
Positive	56	5	61
Negative	11	59	70
Total	67	64	131

The negative predictive value of light reflection rheography was 92 per cent and this degree of accuracy is sufficient to consider using the technique as a screening test for deep venous thrombosis. This figure was obtained with no previous experience with the method and we believe that with increased familiarity of the technique the accuracy rate could be improved. In addition we feel that the technique is not suitable for screening the elderly, those with pre-existing venous disease and conditions which cause low reflectivity as discussed above. No false negative or positive occurred in patients under 55 years old. Light reflection rheography is particularly appropriate for screening pregnant women or patients who would have difficulty attending the radiography department such as postoperative patients or those in intensive care. Outpatients referred to the hospital can sometimes be saved not only the venography but also an unnecessary hospital admission.

Judicious use of light reflection rheography could reduce by half the number of venograms requested for patients with clinically suspected acute deep venous thrombosis. This is equivalent to approximately 100 venograms saved per year in an average district general hospital. At St. Peter's Hospital light reflection rheography is now done before venography in the radiography department by the department's sister or vascular technician. If the light reflection rheography result is negative then the patient is reviewed by a senior doctor and the need for venography is reassessed.

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Histological study of white blood cells and their association with lipodermatosclerosis and venous ulceration

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The number of white blood cells per mm^2 has been determined in serial histological slides taken from punch biopsies of skin from the gaiter region in patients with varicose veins. In eight patients the varicose veins were complicated by lipodermatosclerosis of the skin, and in a further six there was a history of ulceration. In uncomplicated varicose veins there was a median of 6 white blood cells per mm^2, in patients with lipodermatosclerosis there were 45 white blood cells per mm^2, and where there was a history of ulceration, 217 white blood cells per mm^2. No change in white blood cell content was observed after the venous pressure was raised for 30 min by sitting the patient with the lower limb dependent. White blood cell infiltration of the skin is associated with lipodermatosclerotic changes caused by venous insufficiency.

Previous authors have reported that raised venous pressure results in white blood cells becoming ‘trapped’ in the peripheral circulation of the lower limb[1]. Limbs affected by chronic venous insufficiency retain many more white blood cells than normal limbs for the same rise in venous pressure[2]. These observations combined with a capillaroscopic study have led to the proposal that white blood cells play a primary role in the development of venous ulceration[3]. It is suggested that the trapped cells may cause capillary occlusion, and that they are activated releasing superoxide radicals and proteolytic enzymes which damage the microcirculation. The authors’ previous attempts to study this process by radioisotope labelling of leucocytes were unsuccessful owing to the large volumes of blood present in the deep veins of the lower limb (unpublished observations).

The purpose of the present study was to quantify the white blood cell content of the skin in patients with venous disease using conventional histological techniques, and to assess the influence on white blood cell content of raising the venous pressure in the limbs for 30 min.

Patients and methods

Nineteen patients with venous disease proven by vascular laboratory examination were studied. All were undergoing inpatient surgical treatment for varicose veins, five for uncomplicated primary varicose veins and 14 for varicose veins complicated by lipodermatosclerosis of the supramalleolar skin. Six patients with lipodermatosclerosis had previously suffered ulceration of the leg caused by their venous disease, but none had an ulcer at the time of this study Informed written consent to participate in this investigation was obtained from each patient. The study was approved by the hospital ethics committee.

Patients were randomly allocated to be studied after an initial period of 30 min lying supine, or sitting with the leg dependent to raise venous pressure in the lower limb. An area of skin was selected for study and marked. In patients with normal skin this was 5 cm proximal to the medial malleolus. A representative area of lipodermatosclerotic skin was selected in patients with skin changes. Local anaesthesia was obtained by infiltrating 1% lignocaine without adrenaline in an inverted U around the study region A 3 mm punch biopsy of skin was taken. The patient then changed from the lying to the sitting position, or *vice versa*, according to the allocated sequence of study, for a further period of 30 min. A repeat punch biopsy was taken 0 75–1 00 cm from the site of the initial sample. A dry dressing was applied to the skin. After varicose vein surgery, patients wore class III compression stockings (28 mmHg pressure at the ankle) for 2 weeks, as is the authors’ standard practice All punch biopsy sites healed within 2 weeks

Biopsy specimens were preserved in buffered formal saline and processed by conventional histological techniques. Sections 4–5 μm thick were cut using a standard microtome. Every third section was mounted on a glass slide (three sections per slide). These were dried in an oven at 60°C and stained with haematoxylin and eosin The slides were coded so that the clinical details and position of the limb could not be identified by the microscopist. Slides were counted using an orthoplan widefield Leitz Wetzlar (Leitz, Solme, Germany) binocular microscope. Five separate counts were taken of each section. An eyepiece graticule measuring 0 22 × 0 14 mm (at a magnification of × 40) was placed randomly within the section to a maximum depth of 0·5 mm from the epidermis. The white blood cells within the window were counted. No attempt was made to characterize the nature of the white blood cells, which were principally polymorphonuclear leucocytes, or to determine their relationship to blood vessels, as a pilot study suggested that this was unlikely to be reliable A total of 2280 sections were counted. One author (H.J.S.) undertook all microscopic evaluation of specimens When counting was complete the identification code was deciphered to permit analysis of the data Statistical analysis was performed using Minitab 5.1, employing the Mann–Whitney *U* test, as the data are not of a Gaussian distribution

Results

The median white cell count in sections from normal limbs was 6·2 (interquartile range 4·9–7·0) cells per mm^2, from lipodermatosclerotic limbs 45 (interquartile range 26–178) cells per mm^2, and from lipodermatosclerotic limbs with a history of ulceration 217 (interquartile range 107–224) cells per mm^2 in the supine position. These differences are statistically significant; all patients with normal skin had fewer white blood cells per unit area than the patients with skin changes (*Figure 1*).

No change in white blood cell distribution was observed following 30 min sitting. The median white blood cell count in sections from normal limbs was 5·8 (interquartile range 3·5–8·3) cells per mm^2, from lipodermatosclerotic limbs 45 (interquartile range 27–167) cells per mm^2, and from lipodermatosclerotic limbs with a history of ulceration 193 (interquartile range 95–256) cells per mm^2 in the dependent position.

Discussion

Some of the histological changes present in the skin in venous disease have been described in papers which addressed abnormalities of the capillaries and presence of fibrin cuffs[4]. Descriptions of liposclerotic skin suggest that there is evidence of inflammation with a dermal infiltration of white blood cells[5],

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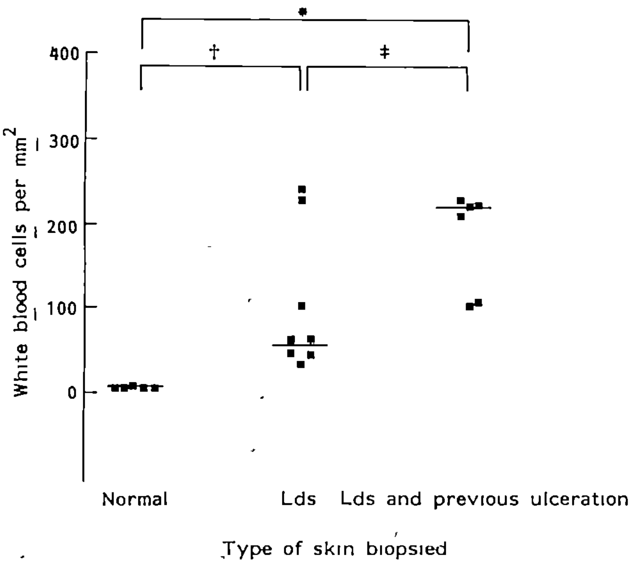

Figure 1 *Scattergram (with group median values) of the individual patient's white blood cell counts per mm^2 in the lying position. Bars show median values. Lds, lipodermatosclerosis.* *P=0·004, †P=0·03, ‡P=0·008 P *value obtained using Mann–Whitney* U *test*

but no quantitative data have yet been published which define the exact abnormality. Until recently theories suggesting a pathological mechanism by which ulceration might occur in venous disease have concentrated on the means by which the skin might be deprived of its oxygen supply and have centred on anomalies of the dermal capillaries[6]. Originally this was suspected in the early 20th century when it was suggested that low oxygen levels in the veins of the leg might result in ulceration[7]. Subsequent investigations have failed to confirm low oxygen tensions in varicose veins, in fact proving the converse, including a recent study of our own[8,9]. This persisting need to ascribe tissue necrosis to hypoxia has been without satisfactory direct evidence of reduced oxygen tensions in the skin, relying in recent years on transcutaneous measurements of oxygen tension. Other pathological phenomena in the skin seem to have been ignored.

Recently it was observed that white blood cells may become 'trapped' in the tissues of the lower limbs of normal subjects in response to raised venous pressure produced by sitting with the lower limbs dependent[1]. It was suggested from these observations that this process might be important in patients with venous disease. A study was carried out comparing the white blood cell 'loss' in response to raised venous pressure in patients with venous disease and normal subjects. Examination of the dermal capillaries in the supramalleolar region following a period of raised venous pressure suggested that some damage was caused to the capillary bed during standing in patients with deep venous insufficiency, but not in normal subjects. This led to a hypothesis in which white blood cells became attached to capillary endothelium, producing ischaemia and became activated causing damage to endothelium as well as other tissues.

In the present study there were certainly many more white blood cells in the skin in patients with liposclerotic changes. This is particularly significant because all patients in this series were suffering from varicose veins requiring surgical treatment. Clearly this observation confirms that lipodermatosclerosis is also an inflammatory condition, and should perhaps more correctly be called 'lipodermatitis'. It is interesting that patients with a previous history of ulceration showed a greater white blood cell content in the skin, indicating that the inflammatory response may be closely related to the process that eventually causes ulceration. No increase in white blood cell count was observed after the patients sat for 30 min, indicating that the effects of short-term venous hypertension could not be detected by this technique. It seems likely that the white blood cell count in the skin is raised substantially when venous disease affects the skin so that the cells trapped in such a short period do not influence the total white blood cell content.

This study has shown that there is an increased number of white blood cells in the skin of patients with venous disease resulting in lipodermatosclerosis. Those patients whose disease was sufficiently severe to result in ulceration had significantly more white blood cells than patients in whom ulceration had never occurred. Because no patient with an ulcer was studied these differences are probably attributable to the effects of persistently raised venous pressure, rather than infection or inflammation surrounding an ulcer. Patients had not received any treatment that might influence the venous insufficiency before this investigation, so the increased white blood-cell count persisting after venous ulcer healing is a reflection of the severity of the venous disease that resulted in the skin changes or ulceration. This study cannot demonstrate whether the increased white blood cell content of the skin is a cause or result of the skin changes The destructive proteolytic enzymes and superoxide radicals that such cells may release are possible candidates for the agents of tissue destruction, as they are in critical ischaemia[10]. In addition, some white blood cells have the capability to release mediators of inflammation (such as the cytokines, tumour necrosis factor and interleukin 1) and leukotactic agents (such as leukotrienes) The data in this paper suggest that the metabolic activity of the white blood cells should be investigated to determine if they play any part in the development of venous ulceration.

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Oesophageal transection and oesophagogastric devascularization in patients with thrombophilia and oesophageal varices

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Thrombophilia describes a spectrum of primary, coagulative disorders which promote thrombosis. The prevalence of these disorders may be as high as one in 250 of the general population. The disorders are the result of reduced protein concentration (type 1) or reduced biological activity (type 2). Increased levels of specific inhibitors in childhood compensate for the inherited abnormalities and thus these patients present in adult life. Patients with these disorders may require long-term anticoagulant therapy. We present two patients whose thrombophilic disorders were associated with and complicated by symptomatic oesophageal varices.

Case reports

Case 1

A 40-year-old man was referred to Glasgow Royal Infirmary with haematemesis Bleeding oesophageal varices were diagnosed at endoscopy and these were treated by injection sclerotherapy. His liver function tests were normal and his Child's classification was grade A. He gave a history of a myocardial infarction 2 years previously and it was noticed that his coagulation showed both intrinsic and extrinsic defects. Abdominal ultrasound scans were suggestive of fatty liver disease (confirmed by biopsy) and of portal vein thrombosis, subsequently substantiated by angiography

Further haematological investigations revealed a plasminogen deficiency as the cause of his thromboses and this necessitated long-term anticoagulant therapy. Because of a high risk of further variceal haemorrhage he underwent oesophageal transection and oesophagogastric devascularization. Four years after surgery he has had four further venous thromboses but only one small haematemesis secondary to minor residual varices which were easily treated by injection sclerotherapy.

Case 2

A 32-year-old man presented with lower abdominal pain and ascites Abdominal ultrasound examination suggested parenchymal liver disease associated with hepatic vein and inferior vena caval thrombosis Liver biopsy showed micronodular cirrhosis with no histopathological features to suggest its aetiology. His Child's classification was grade B Further studies of coagulation indicated disorders of both the intrinsic and extrinsic pathways, and protein C deficiency was eventually elucidated. He was commenced on long-term anticoagulant therapy.

Within 6 months of presentation the patient had had two major haematemeses from oesophageal varices and at that time his blood levels of anticoagulants were in the therapeutic range Because of the risk of further rebleeding and the need for continued anticoagulant therapy he underwent oesophageal transection and oesophagogastric devascularization. No further bleeding has occurred in the 6 months following this procedure.

Discussion

Protein C is a vitamin K-dependent plasma protein which was first isolated by Stenflo in 1976. It inhibits coagulation by the inactivation of prothrombin and factors V and VIII on the platelet surface[1]. The control of fibrinolysis has as its end-point the conversion of plasminogen to plasmin, and thus fibrin digestion. Although not completely elucidated, fibrinolysis is controlled by three systems: the intact coagulation pathway, prourokinase, and a tissue plasminogen activator[1]. Deficiency of plasminogen has, like protein C deficiency, a propensity to promote coagulation

The clinical features of these conditions are spontaneous major vessel thromboses between the ages of 15 and 40 years. By the age of 50 years, 85 per cent of individuals with protein C deficiency have had a major thrombosis[1]. Treatment for major deficiencies ideally involves specific factors (produced by genetic engineering techniques or improved plasma fractionation), but at present anticoagulation remains the mainstay of therapy.

Patients with thrombophilia requiring anticoagulation who develop oesophageal varices are at greater risk of variceal rebleeding because of the anticoagulation. There are a number of therapeutic options. Shunting will lower portal venous pressure and control variceal haemorrhage. Langer *et al.*[2] have demonstrated lower rates of encephalopathy but higher rebleeding rates with the distal splenorenal shunt compared with an end-to-side portacaval shunt In the presence of thrombophilia the risk of shunt thrombosis is increased, even with therapeutic anticoagulation, and this precludes the use of these procedures in the majority of cases. This is illustrated by our first patient who developed four further venous thromboses despite adequate anticoagulation. Endoscopic sclerotherapy is hazardous in the presence of anticoagulation, and with reported rebleeding rates of 37 per cent[3] and 53 per cent[4] we believe that it is rarely an option in this context.

Oesophageal transection using the circular stapling gun combined with oesophagogastric devascularization[5] appears to be the best option for these patients with a low risk of rebleeding, even in the presence of full anticoagulation, and no increased risk of encephalopathy. However, all of these patients must be carefully assessed in conjunction with a haematologist and the treatment must be individualized.

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Long-term follow-up of elderly patients with locoregional breast cancer treated with tamoxifen only

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One hundred and thirteen women aged 70 years or more with locoregional breast cancer were treated with tamoxifen alone as primary treatment. They were followed for a minimum of 5 years. Complete response occurred in 38 women, partial response in 17, no change in 34 and progressive disease in 24. Where progressive disease occurred, or where patients relapsed after an initial response, the most suitable conventional therapy was given. The actuarial 5-year survival rate was 49·4 per cent for all patients and was much higher (92 per cent) in those showing an initial complete response. Seventy patients (61·9 per cent) were not controlled by tamoxifen alone to death or most recent follow-up. Tamoxifen provides an alternative treatment for operable breast cancer in older women in the short term and may be particularly suitable for those with concurrent disease or who are unwilling to undergo surgery. The low morbidity rate from tamoxifen must be balanced against the need to maintain close follow-up. In the medium to long term, sole primary treatment by tamoxifen delays more definitive therapy.

The management of breast cancer in the elderly has been reviewed recently by Cox[1] and the optimal treatment ranges from radical surgery, regardless of age, to medical treatment alone.

A conservative approach has been reported in England[2], Sweden[3] and Scotland[4,5] where elderly patients with locoregional breast cancer have been treated with tamoxifen alone as primary treatment. This offered an alternative to surgery for elderly women with concurrent disease or to those who may be reluctant for hospital admission. Because the proportion of oestrogen receptor-positive tumours and the oestrogen receptor content increase with age[6–9], elderly patients may be more likely to respond to tamoxifen.

Two prospective randomized trials using tamoxifen in the elderly have been reported with contradictory conclusions. Robertson *et al* [10] randomized 135 patients with breast cancer to receive either wedge mastectomy with excision of symptomatic lymph nodes or tamoxifen alone with no surgery. There was no difference between the survival rates of the two groups but, after 2 years, a significantly higher percentage of the tamoxifen group required surgery for local progression of the disease This led to the conclusion that optimum treatment for elderly patients should include both surgery and tamoxifen. Gazet *et al.*[11], after randomizing 116 elderly patients to receive surgery or tamoxifen, found no difference in survival rates or the time to progression of disease and concluded that tamoxifen could be the first-line treatment. Some criticisms have been made of this study[12–14], including whether wide local excision of the tumour alone provides adequate treatment.

Bradbeer and Kyngdon[2] treated 161 patients over the age of 70 years with tamoxifen alone Sixty-one per cent showed objective regression of the disease with a complete response occurring in 27 per cent. The 5-year actuarial survival rate was 70 per cent, significantly higher than the survival rate of 42 per cent seen in an earlier series of 103 patients treated at the same hospital by surgery, radiotherapy or oestrogens. In a similar pilot study, Preece *et al.*[5] reported that, in a series of 67 women over the age of 75 years, 49 (73 per cent) responded sufficiently well for treatment to be continued after the first follow-up visit This study considers the long-term follow-up of the same series with patients treated more recently.

Patients and methods

Between 1978 and 1984, 113 elderly patients presented to the breast clinic at Ninewells Hospital, Dundee with operable, locoregional breast cancer (stages I–III) and were treated wih 20 mg tamoxifen twice daily as sole primary treatment This treatment was given because of the patient's age or unwillingness to undergo surgery or because surgery was contraindicated by concurrent medical conditions. Diagnosis was confirmed by cytology of a fine needle aspirate in all but two cases which were diagnosed on mammography alone Staging tests, including bone and liver scans, radiographs of chest, lumbosacral spine and pelvis, and bone and liver function tests were carried out to exclude the possibility of metastatic spread

Patients were followed up monthly for 6 months and then 3-monthly. Where possible they were seen by the same consultant at each clinic visit The tumour was measured using calipers and nodes were palpated at each visit. After 3 months, response was assessed according to UICC criteria[15]. complete response, partial response, no change, and progressive disease 'Best ever response' was also assessed for each patient using the definition of 'the maximum reduction in tumour size achieved at any time during tamoxifen treatment' Minimum follow-up was 5 years.

The cause of death was established by consulting death certificates, autopsy reports, cancer registry records, case notes and questionnaires sent to general practitioners. In cases where breast cancer was recorded on the death certificate but not given as the underlying cause of death, the disease was considered to be under control at death if there had been no evidence of recurrence or metastases at the most recent follow-up visit, provided this was within 3 months of death In equivocal cases, where there were no recent clinic visits and where breast cancer was given on the death certificate, it was assumed that breast cancer had contributed to the death

The patients were all aged 70 years or more (range 70–93 years) Two-thirds (68 per cent) were aged between 70 and 79 years, and one-third (32 per cent) was aged 80 years or more Their stages at presentation are shown in *Table 1*.

Results

Of the 113, 89 (78·8 per cent) responded for at least 6 months. The numbers (and percentages) of patients in each response category are shown in *Table 2*, the response shown being the 'best ever' obtained. *Table 3* shows the response in relation to stage at presentation.

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Table 1 *Stage at presentation of 113 patients with locoregional breast cancer*

Stage	No. of patients
I	6 (5·3)
II	75 (66·4)
III	32 (28·3)

Values in parentheses are percentages

Table 2 *'Best ever response' in 113 patients with breast cancer treated with tamoxifen alone*

	No. of patients
Complete response	38 (33·6)
Partial response	17 (15·0)
No change	34 (30·1)
Progressive disease	24 (21·2)

Values in parentheses are percentages

Table 3 *Response by stage at presentation*

	Stage I	Stage II	Stage III	Total
Complete response	4	26	8	38
Partial response	1	10	6	17
No change	1	26	7	34
Progressive disease	0	13	11	24
Total	6	75	32	113

Time to response

There was considerable variation in the time taken to achieve a complete response, ranging from 3 to 37 months (median 9 months) as shown in *Figure 1*.

Duration of response

The duration of response known to date is shown in *Figure 2* which includes data from patients who are still responding and those who responded to death where this was from causes other than breast cancer. The median known duration of response of 50 months for those showing a complete response is significantly longer (Mann–Whitney U test, $P<0.05$) than for those with a partial response (18 months) or where there was no change (21 months)

Figure 3 shows the actuarial local control rate with tamoxifen alone up to 6 years for all those who responded (i.e. those with complete response, partial response and no change). Local control was maintained in nearly one-third of the patients for 5 years. The actuarial local control rate in relation to response category is shown in *Figure 4*. At 5 years, the percentage with local control among those showing a complete response was considerably higher (87 per cent) than for other responders (partial response 10 per cent, no change 23 per cent).

Outcome after minimum follow-up of 5 years

Of the 89 patients who responded initially, 46 subsequently relapsed, of whom 37 went on to other treatment. Eighteen patients received surgery alone, one had a combination of surgery and radiotherapy, four had radiotherapy only and 13 went on to second-line endocrine treatment. Second-line treatment is under review in one patient. Nine patients received no further therapy other than for treatment of symptoms The outcome for all responders is shown in *Table 4*. Twenty-four patients had disease progression from the outset on tamoxifen and in 23 the management was changed. One patient is alive and well, five died from intercurrent disease and 18 died from breast cancer

Figure 5 shows the actuarial local control rate achieved overall by the combination of tamoxifen and subsequent management: many of the relapsed responders who were given a second line of management subsequently had good control. After 5 years, more than half of the patients achieved local

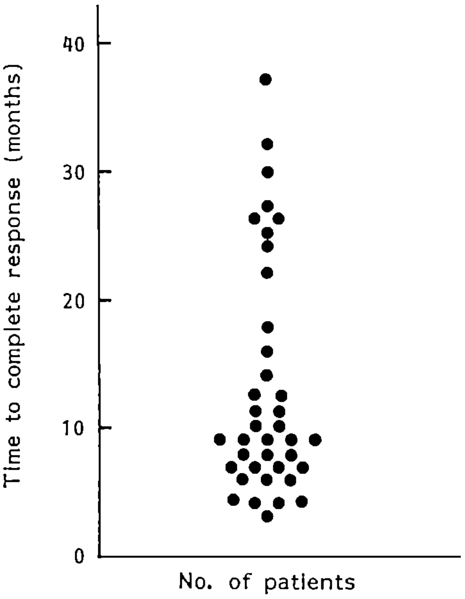

Figure 1 *Time taken for breast cancer patients to achieve a complete response to tamoxifen*

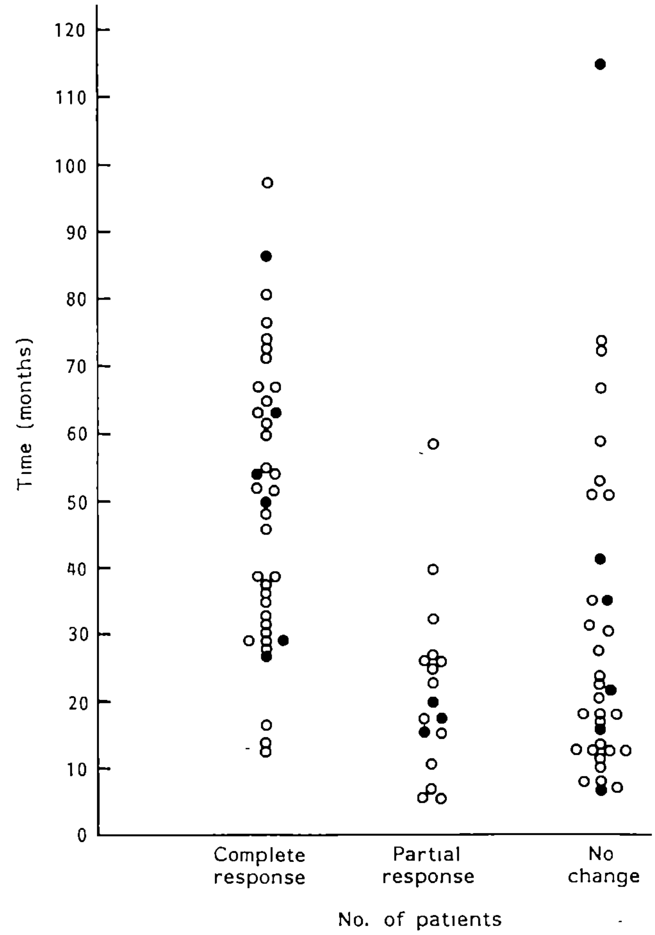

Figure 2 *Known duration of response to tamoxifen in 'best ever' category* (○), *Still responding, or responded then relapsed;* (●), *responded until death from causes other than breast cancer*

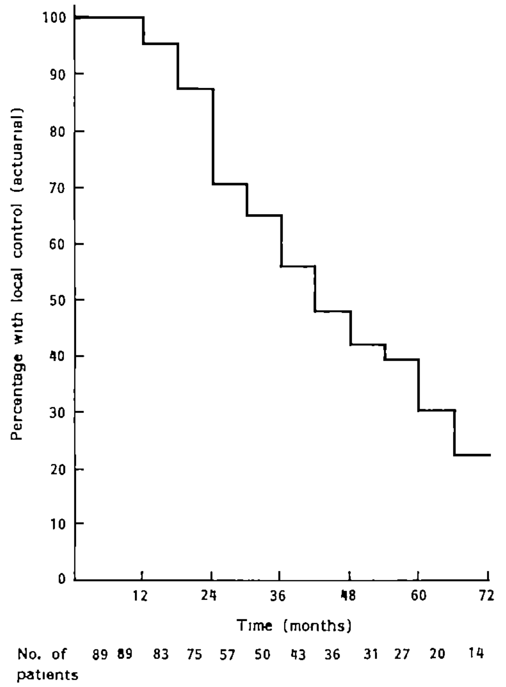

Figure 3 *Actuarial local control rate of breast cancer treated with tamoxifen alone in all tamoxifen responders*

control; for those with an initial complete response, nearly 90 per cent were still controlled at 5 years. Seventy (61·9 per cent) patients were not controlled by tamoxifen alone to death or last follow-up including the 24 who failed to respond to tamoxifen from the outset and 46 who responded initially but later relapsed. Most of these patients went on to different management and 25 are alive and well, the rest have died from intercurrent disease.

Survival

Figure 6 shows the actuarial survival rate in relation to response. The actuarial 5-year survival rate was 49·4 per cent for all patients and was highest for those showing an initial complete response (92 per cent) (partial response 72 per cent, no change 63 per cent, progressive disease 15 per cent) *Figure 7* shows that there was no difference in the actuarial survival rate up to 5 years of the younger age group (70–79 years) compared with the older patients (80 years and over)

Discussion

The use of tamoxifen may provide an acceptable alternative to surgery in the elderly providing that it does not delay relapse until a time when the patient is less fit for surgery than at presentation or until the tumour has become unmanageable.

Amsterdam *et al* [16] reported a series of 100 women over the age of 70 years who were treated by simple or modified radical mastectomy: most received postoperative radiotherapy and some had adjuvant hormonal treatment with no operative mortality and negligible morbidity. Amsterdam *et al.* concluded that elderly women should be treated by surgical methods that offer the best chance of cure, regardless of age. This view was also proposed by Haagensen[17], Davis *et al.*[18] and Hunt *et al.*[19] In a series of 465 patients aged over 70 years treated by surgery, Svastics *et al.*[20] reported five deaths (1 per cent) Margolese and Foster[21] reported a surgical mortality rate of 1–2 per cent in elderly women treated by mastectomy. Kesseer and Seton[22] argued that all patients with operable breast cancer should be treated by surgery but that this should be less radical in patients over the age of 80 years whose life expectancy is less than 8 years or where there is a significant operative risk.

Osborne *et al* [23] have shown that MCF-7 tumour cells remain viable after long periods of growth suppression by tamoxifen and tumour cells are presumably still present in patients who have shown a complete response to tamoxifen. Tamoxifen is assumed to act in a cytostatic rather than cytocidal way[24].

This study shows that control of breast cancer can be achieved in some patients with a long period of remission using tamoxifen. The median survival of these patients was 5 years but more than half of the responders had relapsed locally by then. Overall, 61 9 per cent of patients were not controlled to death or last follow-up The rate of relapse is steady over the years (*Figure 3*) and patients managed medically need continued regular follow-up so that relapse can be detected early and local control is not lost. This need may be burdensome to the patient and possibly to clinic facilities, and elderly patients who relapse may have become frail and less fit for subsequent therapy

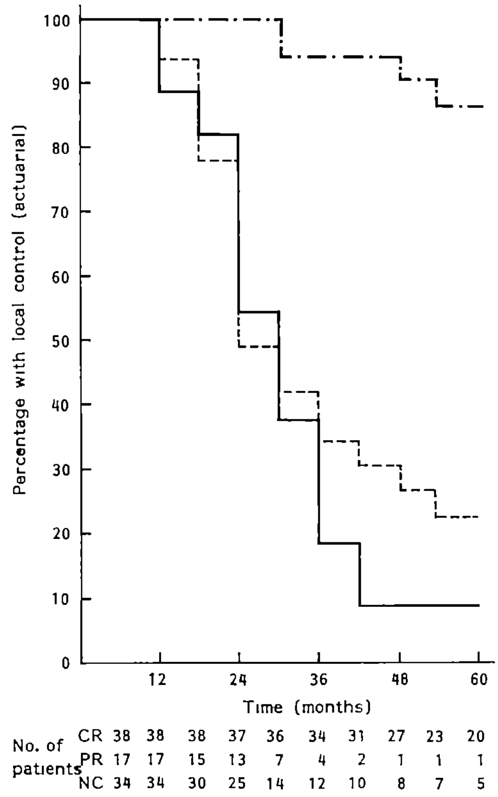

Figure 4 *Actuarial local control rate of breast cancer treated with tamoxifen alone in relation to response category.* (–·– –), *Complete response* (*CR*), (——), *partial response* (*PR*), (– – –), *no change* (*NC*)

Table 4 *Outcome for all responders*

	No of patients
Total responding for at least 6 months (complete response, partial response and no change)	89
Alive and still responding	16
Responded until death from other causes	26
Relapsed after initial response (management changed)	37
Alive and well	9
Died from other causes	10
Alive with progressive disease	2
Died from breast cancer (including two perioperative deaths)	16
Died from breast cancer (with no change of management other than palliative)	9
Lost to follow-up	1

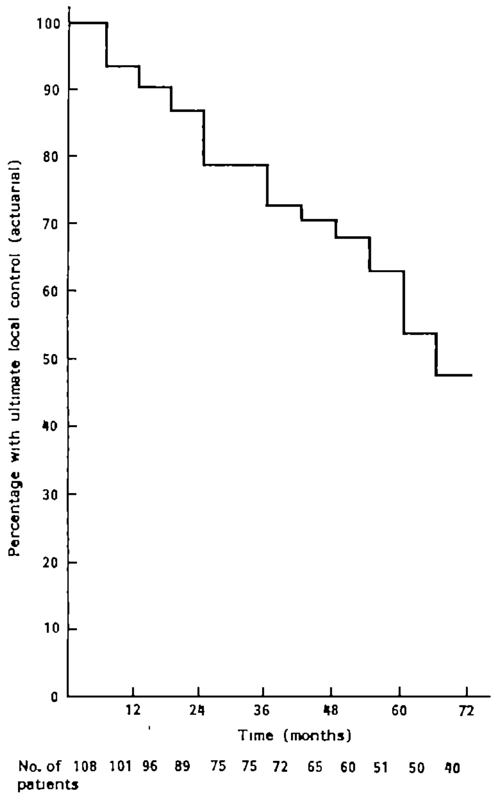

Figure 5 *Actuarial local control rate achieved overall by combination of tamoxifen and subsequent management*

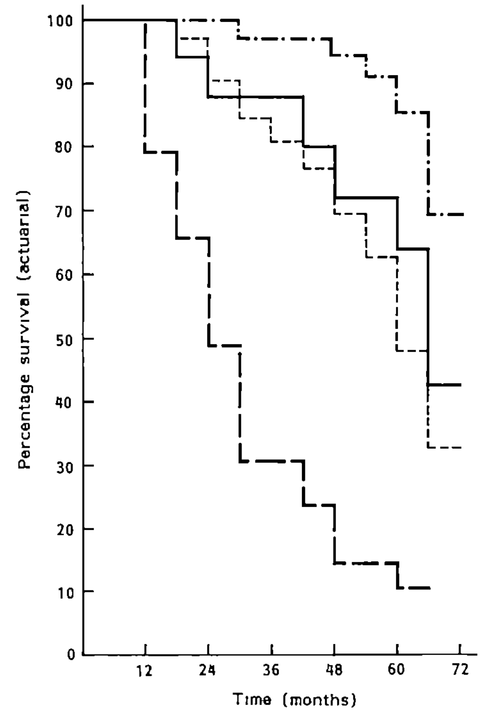

Figure 6 *Actuarial survival rate in relation to response category.* (–·– –), *Complete response* (*CR*); (——), *partial response* (*PR*); (– – –), *no change* (*NC*), (— — —), *progressive disease* (*PD*)

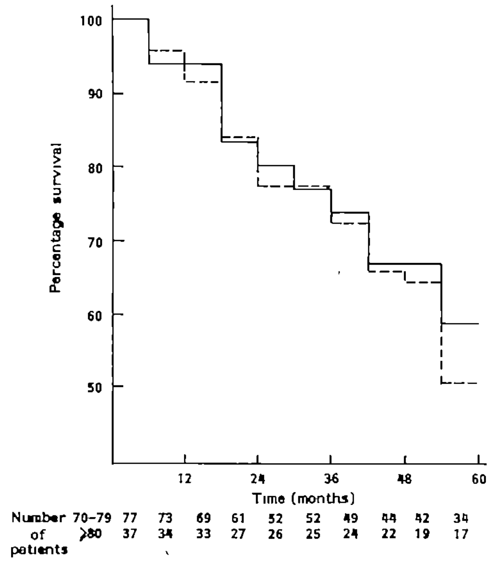

Figure 7 *Actuarial survival rate in relation to age at start of treatment.* (– – –), *70–79 years*, (——), *≥80 years*

Where an elderly patient is frail or suffers from concurrent disease likely to affect her longevity, the period of remission with tamoxifen may continue until death from other causes. About 62 per cent of the women studied here were not controlled to death or last follow-up and caution must be exercised about the use of tamoxifen as initial sole primary treatment for all elderly patients. Fit patients in their seventies and eighties may have a longer disease-free interval and survival if they are treated with standard locoregional modalities such as mastectomy or tumourectomy with radiotherapy, followed by the use of adjuvant tamoxifen This would avoid the more frequent follow-up that is required if treatment is by tamoxifen alone.

In the short term, tamoxifen appears to be a valid alternative to conventional management of operable breast cancer in older women, particularly because of its low toxicity. Low morbidity from tamoxifen must be balanced against the need to maintain close follow-up. In the medium to long term, primary treatment by tamoxifen appears to delay more definitive therapy.

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Mammography in the management of patients with small breast cancers

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Findings on mammography resulted in a change of treatment policy in 17 of 200 patients with small breast cancers ($T_1/T_2 < 4$ cm, N_0/N_1, M_0). Twelve patients were considered unsuitable for conservation therapy because of mammographic evidence of either extensive in situ *carcinoma or more than one focus of invasive carcinoma. These patients were treated by mastectomy and histology confirmed widespread* in situ *carcinoma or multifocal/multicentric invasive carcinoma. Seven patients were found to have unsuspected contralateral lesions on mammography, of which five were subsequently shown to be malignant. Routine preoperative mammography is essential in the management of patients with small breast cancers.*

Not all patients with small breast cancers are suitable for treatment by breast conservation. Where tumours are incompletely excised and where there is more than one focus of invasive disease or widespread *in situ* changes, the recurrence rates are unacceptably high[1,2]. This study set out to determine whether mammography identifies those patients with small palpable breast cancers who are unsuitable for breast conservation and whether mammography of the other breast detects significant numbers of asymptomatic contralateral carcinomas.

Patients and methods

Two hundred patients aged 70 years or less, with a single palpable breast cancer measuring less than 4 cm, not locally advanced and without extensive nodal disease or systemic metastases, were studied. These patients were a consecutive series presenting to the University Department of Surgery Breast Unit during 1987 and 1988 Fourteen patients had their breast cancer detected on screening and the remaining women were symptomatic All patients on clinical examination would have been suitable for conservation therapy within the protocol of the Scottish Breast Cancer Conservation Study[3] All patients had mammography before a decision on definitive management. Mammography (single oblique view in women aged 35–39 years, two views in older women) was performed before the initial clinic visit in 192 patients. Further views or magnification mammograms were performed in 18 of these patients. Mammograms were reported by one of three consultant radiologists with knowledge of the initial clinical findings. The remaining eight patients were 34 years of age or less and had two-view mammography after a diagnosis of carcinoma was confirmed on fine needle aspiration cytology. These mammograms were reported with the knowledge that the patient had carcinoma

It is our practice to advise mastectomy for patients with proven breast cancer who mammographically are considered to have widespread *in situ* carcinoma or multifocal/multicentric invasive disease Other non-palpable suspicious lesions in the same breast and suspicious non-palpable lesions in the opposite breast are excised using a needle localization technique[4]. Those patients subsequently shown to have synchronous bilateral breast cancer are advised to have bilateral mastectomy. Patients with a small breast cancer whose mammograms show none of these features are offered conservation treatment, which can include surgery, radiotherapy and systemic therapy. Surgery consists of excision of the tumour mass with a 1 cm margin of surrounding normal breast tissue. All patients have axillary node sampling or clearance as part of a prospective trial Within the Scottish Conservation Study those patients with histologically clear excision margins are treated systemically on the basis of nodal and oestrogen receptor status Postmenopausal patients and premenopausal node-negative patients are randomized to receive either no other treatment or postoperative radiotherapy Premenopausal node-positive patients all receive radiotherapy.

Results

In 149 patients mammograms showed a localized malignant lesion, in 32 patients no suspicious lesion was identified and in the remaining 19 patients mammography detected abnormalities not suspected on initial clinical examination. Six of these 19 patients had a localized malignant mass lesion associated with an extensive area of microcalcification indicative of *in situ* disease and six patients had more than one malignant mass (four patients having multifocal lesions in the same quadrant and two having multicentric lesions in different quadrants). A further seven of the 19 patients were reported to have a malignant lesion in the symptomatic breast and a suspicious lesion in the contralateral breast. Overall, mammography indicated that 168 of the 200 palpable breast cancers were malignant – a sensitivity of 84 per cent.

The mammographic findings were known at admission to hospital when all patients were re-examined. In two of the six patients considered to have multifocal disease and in two of the seven with a contralateral mammographic lesion, a further clinical abnormality was detected. Fine needle aspiration cytology from these four lesions yielded malignant cells from three and an aspirate from the contralateral breast in a patient with microcalcification was acellular.

Mastectomy was performed in the 12 patients with mammographic evidence of widespread *in situ* carcinoma or more than one focus of invasive carcinoma. Subsequent histology confirmed that the six patients with widespread suspicious microcalcification had widespread multifocal or multicentric *in situ* carcinoma, and that the six patients suspected of having multifocal or multicentric invasive carcinoma did have more than a single invasive focus of carcinoma Of the seven contralateral mammographic lesions, one was a mass lesion and was palpable and yielded malignant cells on aspiration. The other six were areas of microcalfication and excision after needle localization showed that four of these six lesions were *in situ* carcinomas and that the other two were benign. A summary of the results is presented in *Table 1*.

Discussion

Patients with invasive breast cancer treated by local excision and radiotherapy who have widespread *in situ* disease or who have residual invasive carcinoma are at high risk of subsequent local recurrence[1,2]. This study shows that mammography accurately identifies some of those patients with widespread *in situ* disease and others with multifocal and multicentric invasive carcinoma Because of the high risk of recurrence after breast

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Table 1 *Summary of mammographic findings in 200 patients with palpable breast cancers*

Mammographic diagnosis	No. of patients
Localized mass (malignant mass lesion)	149
No suspicious mass lesion	32
Mass+adjacent malignant microcalcification*	6
Multiple malignant mass lesions	
Two lesions*	5
Three lesions*	1
Mass+contralateral malignant mass lesion*	1
Mass+contralateral suspicious microcalcification†	6
Total	200

* Subsequently confirmed on histology, † four of six *in situ* carcinoma on histology

conservation in these patients, it is our practice to perform a mastectomy for extensive *in situ* or multifocal and multicentric disease. Open biopsy with frozen section could be used to establish a histological diagnosis before mastectomy in patients with mammographic suspicion of multifocal or multicentric disease. Alternatively, a stereotactic fine needle aspiration cytology of non-palpable lesions might establish a diagnosis.

The incidence of multifocal and multicentric carcinoma in the breast is known to be high[5], the exact incidence depending on the definition. Fisher *et al.*[6] in a series of 904 patients with invasive breast cancer reported a 13·4 per cent incidence. Combining the patients in the present series with extensive *in situ* carcinoma and those with more than a single focus of invasive carcinoma, mammography demonstrated multifocal or multicentric disease in 12. Mammography does not identify all patients with multifocal and multicentric disease. Invasive lobular carcinomas, for example, are frequently not seen on mammography and have the highest incidence of multifocality and multicentricity[6].

Between 0·2 and 2 per cent of patients have symptomatic simultaneous bilateral breast cancer[7,8] and studies where contralateral biopsies are performed indicate that the true incidence is many times higher[9,10]. This incidence of impalpable breast cancers in the contralateral breast adds credence to our view that bilateral mammography is essential in the assessment of all patients with breast cancer.

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Gunshot wound of the abdomen: role of selective conservative management

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This prospective study includes 146 patients with gunshot wounds of the abdomen. One hundred and five patients (72 per cent) had an acute abdomen on admission and were operated on immediately. The remaining 41 patients (28 per cent) had minimal or equivocal abdominal signs and were observed with serial clinical examinations. Seven of the observed patients needed subsequent laparotomy, but there was no mortality or serious morbidity. Had a policy of mandatory exploration for abdominal gunshot wound been applied the incidence of unnecessary or negative laparotomies would have been 27 per cent. By using a policy of selective conservatism this figure was only 5 per cent. We suggest that abdominal gunshot wounds should be assessed and managed exactly like knife wounds. Physical examination is reliable in detecting significant intra-abdominal injuries. Many carefully selected patients with abdominal gunshot wounds can safely be managed non-operatively.

The role of selective conservatism in stab wounds of the abdomen is widely accepted. This policy has not gained popularity in the management of abdominal gunshot wounds and the standard practice is mandatory exploration, irrespective of clinical signs and symptoms. Scanty reports on the possible role of selective conservatism in gunshot wounds have been ignored by most trauma centres. It has been a long-standing practice in this unit not to distinguish between knife wounds and low velocity gunshot wounds of the abdomen, and to manage both types of injury with selective conservatism.

Patients and methods

A prospective study was performed over 20 months (from July 1988 to February 1990) at Baragwanath Hospital, Johannesburg. Patients with obviously superficial wounds and those who died in the emergency department or in the operating theatre were excluded. The management protocol remained unchanged during the period of the study and was as follows. All patients with abdominal gunshot wounds presenting with either an acute abdomen (rigidity, rebound tenderness, tenderness away from the entrance wound) or rectal bleeding, or blood in the nasogastric tube, were operated on immediately. Preoperative investigations, such as chest and abdominal radiography and urinalysis, were performed only on haemodynamically stable patients. A third generation cephalosporin was started before operation and continued for 24 h after operation. If there was colonic involvement the antibiotic prophylaxis was continued for 48 h.

Patients with minimal or equivocal abdominal signs were managed conservatively, irrespective of the site of entrance or exit of the bullet. Similarly, patients with mild shock responding to intravenous resuscitation were observed if the abdomen was soft and not tender. All patients selected for conservative management had an intravenous line established, a nasogastric tube inserted, chest and abdominal radiographs taken and urinalysis performed. Intravenous pyelography was reserved for marked haematuria. Peritoneal lavage or computed tomography was not performed on any of the patients. No prophylactic antibiotics were given. Observation included regular clinical assessment, preferably by the same surgeon, and hourly blood pressure and pulse rate recordings. If signs of an acute abdomen developed, an operation was performed. Otherwise the patient was discharged after 2–3 days to outpatient follow-up. The policy of observation did not apply to patients in coma or to those having a general anaesthetic for other reasons. These patients were subjected to a laparotomy irrespective of abdominal signs.

Results

One hundred and forty-six patients fulfilled the criteria for inclusion in the study. The mean age was 28 years (range 14–61 years) and 97 per cent of the patients were men. The mean time from injury to admission was 100 min, with 50 per cent of the patients being admitted within 60 min of injury, 70 per cent within 90 min and 78 per cent within 120 min. In 68 per cent of cases there was an exit wound and in the remaining 32 per cent the bullet remained lodged in the body. In 74 per cent the bullet had entered through the anterior abdomen and in the other 26 per cent the entrance was in the back.

One hundred and five patients (72 per cent) had signs of an acute abdomen and were operated on immediately. Significant intra-abdominal injuries requiring repair were found in 99 (94 per cent) patients. One patient had a liver laceration that did not require suturing and five (5 per cent) patients had a completely negative laparotomy. There was a mean of 2·1 injured organs with a mean of 4·4 significant lesions per patient. The most commonly injured organs were the small bowel (57 per cent of patients), the colon (43 per cent), the stomach (23 per cent) and the liver (21 per cent).

Forty-one (28 per cent) patients had minimal or equivocal abdominal signs and were selected for observation. In 16 (39 per cent) the bullet was still in the patient. In 12 (29 per cent) cases the bullet had entered through the back and in the other 71 per cent it entered through the anterior abdomen. Forty patients were haemodynamically stable and only one patient with associated chest injuries was in shock (systolic blood pressure 75 mmHg). One patient who was shot in the suprapubic area presented with gross haematuria and the cystograms showed extraperitoneal extravasation. This patient was successfully managed without operation using bladder catheterization. Seven patients developed abdominal signs at a later stage (from 4 h to 4 days after admission) and needed a laparotomy. In all seven patients there was a significant injury requiring repair. The injured intra-abdominal organs included the colon (three patients), the small bowel (three patients) and the liver (one patient). The patient with the 4-day delay in diagnosis inadvertently received prophylactic antibiotics during the period of observation, and it is possible that this might have been a contributing factor. There was no mortality, but

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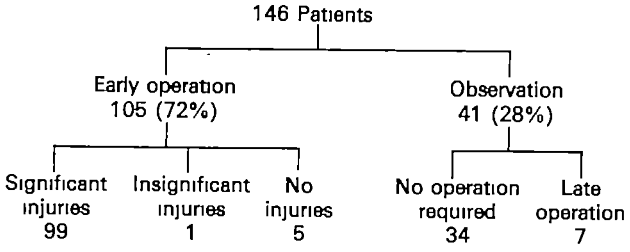

Figure 1 *Management of 146 patients with gunshot wound*

Table 1 *Accuracy of clinical examination in stab wound and gunshot wound of the abdomen*

	No. of patients	Overall accuracy (%)	False positives (%)	False negatives (%)
Anterior abdominal stab wounds*	651	93·9	3·2	2·9
Posterior abdominal stab wounds†	230	95·2	2·6	2·2
Gunshot wound of the abdomen	146	91·8	3·4	4·8

*From Demetriades and Rabinowitz[12]; †from Demetriades et al[13]

one patient developed wound sepsis with dehiscence and another developed wound sepsis alone. The remaining 34 patients in the group selected for conservative management had an uneventful recovery (*Figure 1*).

Discussion

Although the policy of selective conservatism in stab wound of the abdomen has been widely adopted, its role in gunshot wound is highly controversial. Most trauma centres recommend a mandatory laparotomy irrespective of clinical signs[1–5]. The strong feelings regarding the management of gunshot wounds are clearly demonstrated by expressions such as 'no attempt is made to identify a specific indication for laparotomy other than the presence of a gunshot wound that appears to have penetrated the abdominal cavity'[4] or a laparotomy should be performed 'regardless of physical examination or estimated trajectory'[1] or 'exploratory laparotomy should be performed in all gunshot wounds to the abdomen when even the slightest question of penetration exists'[3].

Two reasons are often quoted to support the policy of mandatory exploration. First, gunshot wound is associated with a high incidence of visceral injury and, second, the initial physical examination is not reliable. There is no argument that the incidence of intra-abdominal injury in gunshot wounds is higher than in stab wounds. In a series of 651 patients with knife injury of the anterior abdomen, the incidence in this hospital of significant intra-abdominal injury requiring surgical intervention was 52 per cent[6]. In stab wound of the back the equivalent figure was 14·8 per cent[6]. In the present series 73 per cent of patients with gunshot wounds (75 per cent of the anterior abdomen and 69 per cent of the back) had significant injury requiring operation. Other series have reported similar figures, ranging from 69·9 to 78·3 per cent[4,7–9] From these figures it becomes obvious that between 20 and 30 per cent of patients with abdominal gunshot wounds may be managed without operation.

Some authors used diagnostic peritoneal lavage for superficial-looking abdominal gunshot wounds with equivocal abdominal signs to detect intraperitoneal injury[7,10]. However, such lavage has been shown to be unreliable in assessing abdominal gunshot wounds. The best documented study was published by Thal *et al.*[8]. In a prospective study of 168 gunshot wounds, the authors performed lavage and laparotomy on all patients. The incidence of false negative lavage was 25·4 per cent. Hollow viscus perforation may not be associated with enough blood loss to give a positive lavage and the white cell count in the lavage fluid may not be raised for the first 2–3 h after injury. Furthermore, blood in the lavage fluid does not necessarily mean significant visceral injury[6].

An estimation of the bullet trajectory has been used in an attempt to predict peritoneal penetration. However, low velocity bullets have an unpredictable trajectory, often following paths of least resistance, e.g. fascial planes. Incorrect assessment of the trajectory means that many patients without peritoneal penetration are subjected to a laparotomy[4].

The second argument in favour of mandatory laparotomy is that the initial physical examination is unreliable in abdomen gunshot wounds. Thal *et al.*[8] reported false negative physical examination in 20·2 per cent and false positive examination in 15·9 per cent of patients. Moore *et al.*[7] found an incidence of 17 per cent of false negative examination. Lowe *et al.*[4] reported that 41·5 per cent of patients with no clinical signs on admission had significant intra-abdominal injury requiring repair.

Contrary to these reports, we believe that the initial examination is, indeed, reliable in assessing abdominal gunshot wounds. In the present series the incidence of false negative examination was 4·8 per cent and of false positive examination was 3·4 per cent. As seen in *Table 1*, in this centre the accuracy of the initial physical examination for gunshot wounds compares favourably with that for stab wounds of the anterior or posterior abdomen[12,13]. It seems illogical to accept that clinical examination is reliable for knife wounds but not for gunshot wounds. In theory, the sensitivity of physical examination for abdominal gunshot wounds should be higher than for knife wounds because the average number of significant intra-abdominal lesions is greater for gunshot wounds. We have been using the policy of selective conservatism for abdominal gunshot wounds for many years and are convinced that the management of these injuries should not differ from that for knife wounds.

The biggest concern regarding selective conservatism is that significant injuries may be missed during the initial examination. However, any significant lesion will be detected during the subsequent clinical reassessments of the patient. It has been shown in numerous studies that this type of delay is not associated with serious consequences[12–14].

The proponents of mandatory exploration often underestimate the importance of a negative laparotomy Although some authors have reported minimal morbidity and mortality, most have reported significant morbidity and even mortality[5,9,15,16]. There can be no argument that general anaesthesia and laparotomy, performed on unprepared patients who often have full stomachs or are drunk, can be dangerous. Furthermore, late complications, such as adhesive bowel obstruction or incisional hernia, should be borne in mind. Medical expenses and lost working days should also be taken into account.

The present study describes selective conservatism, based exclusively on physical examination. The incidence of negative or non-therapeutic laparotomy was 5 per cent. In other studies of mandatory exploration on all abdominal gunshot wounds, the incidence of unnecessary operations ranged from 15 to 26 per cent[4,8,9]. Had we followed such a policy of mandatory exploration the incidence of unnecessary operations would have been 27 per cent. In other series in which some form of selective conservatism was applied by means of diagnostic peritoneal lavage, the analagous figure ranged from 8 to 12 per cent[7,10] In conclusion, abdominal gunshot wounds should be assessed exactly as for knife wounds. We advocate a policy of selective conservatism based on careful initial and subsequent serial clinical examinations.

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Abdominal wall tenderness: a useful sign in chronic abdominal pain

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The outcome in 72 patients with obscure abdominal pain and a positive Carnett's (abdominal wall tenderness) test, seen in one firm's surgical outpatient clinic between 1975 and 1983, was sought by a combination of hospital note retrieval and general practitioner questionnaire. Full follow-up data to date or death were available for 58 (81 per cent) patients and partial follow-up for 14 patients. The study showed that the patients generated a good deal of investigation and a number of surgical procedures but that seldom were their symptoms attributable to serious pathology. Familiarity with the test, taken in the context of a proper history and examination, has been found helpful in assessing such patients and saves the inconvenience, expense and occasional hazard of investigation, and even surgery.

Tenderness in patients with abdominal pain is naturally assumed to be either peritoneal or visceral in origin. Carnett[1], however, in 1926 published his observation that patients with perplexing abdominal pain often had abdominal wall tenderness. To demonstrate the sign, the site of maximum tenderness is found and the patient is then asked to cross arms and sit half-way forward. If repeated palpation elicits greater tenderness the sign is positive. Tenderness reflects the discomfort of distortion by the examining hand of an irritated or inflamed structure. With the abdominal wall tense, palpation hardly affects the peritoneum or underlying viscera, so increased tenderness suggests origin in the abdominal wall itself.

In a previous study[2] of 120 emergency admissions for abdominal pain, 23 of the 24 patients in whom the test was positive were found at laparotomy to have normal abdominal contents, whereas in all other cases of peritonitis the sign was negative – in other words their tenderness had been reduced by tensing the abdominal wall.

The present study examines the outcome in a series of patients with chronic non-specific abdominal pain in whom Carnett's test was positive.

Patients and methods

Between 1975 and 1983 particulars of 72 patients referred to one surgeon at Gloucestershire Royal Hospital (W H F.T) were kept. In 1989 all 70 available hospital records were studied and questionnaires were sent to all the general practitioners involved, except in the cases of four patients known to have died and three with current information already available Sixty-two (95 per cent) of 65 questionnaires were returned. For the two patients with missing hospital notes, information gathered after enlistment had fortunately been recorded on their file cards in a collation study in 1983.

Table 1 shows that the 'partial follow-up' group consisted of 14 patients and included ten patients whose questionnaires were returned saying that the patient had moved but for whom postenlistment hospital records were available. Of the three without returned questionnaires there were postenlistment hospital records for two and one was known to have moved after elective appendicectomy One final patient was reported by the general practice secretary to have moved.

Results

There were 65 women (median age 37 years, range 9–75 years) in the study group and seven men (median age 52 years, range 27–67 years). Symptoms had been experienced for a mean of 2 years before consultation (range from 1 day to 15 years) and the main site of tenderness was the right iliac fossa (61 per cent) with the left iliac fossa (24 per cent) accounting for the majority of the rest

Table 2 lists the investigations performed in 46 of the patients. None was requested in the other 26 patients, mainly because of increasing confidence in the test. An abnormality was found in seven of the 96 largely radiological procedures in the 46 patients investigated but, from the notes, in none was the abnormality considered to account for the pain and no management change ensued. In addition, early in the study period seven patients had such impressive symptoms that laparotomy and appendicectomy seemed justified at the time Histology was normal in two of these patients, showed evidence of previous inflammation in four, and was unrecorded in one. Two further patients who had undergone appendicectomy in the past were, after much discussion and investigation and at their request, submitted to a full laparotomy. In neither case was an abnormality discovered.

Table 3 shows specialist referrals before and after enlistment in the study and illustrates both the multiplicity and variety of complaint with a predominance of gynaecological involvement. The 62 questionnaires reported that 31 (50 per cent) of the patients had suffered previous, concomitant or subsequent backache, and that 21 (34 per cent) patients experienced depression or anxiety Sixteen of the 65 women had undergone hysterectomy before enlistment in the study, and a further five had a hysterectomy after enlistment

Table 4 lists diagnostic events after enlistment in the study and *Table 5* describes the cause of the four known deaths Only in patient numbers 6, 12 and 13 were the signs elicited at consultation almost certainly indicative of the serious underlying pathology subsequently diagnosed, although patient number 1 may be a further example. Patient numbers 12 and 13 had previously had treatment for primary carcinoma and their abdominal symptoms and signs were probably due to the spinal metastases they were later proved to harbour. Pain in patient number 6 probably arose from her pyelonephritic kidney.

Discussion

Having previously discovered the usefulness of the abdominal wall tenderness test in assessing the acute abdomen[2] we have now confirmed its application to the diagnostically perplexing outpatient case The recent experience of the senior author

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Table 1 *Category and source of review information for 72 patients*

	Questionnaire and hospital record information	Hospital record information only	General practice receptionist information	Total	Average follow-up period (years)
Full follow-up	51	7		58	10
Partial follow-up	10	3	1	14	7

Table 2 *Investigations performed in 46 patients as a result of the original referral*

Investigation	No
Pyelography	22
Endoscopy	8
Cholecystography	20
Ultrasonography	10
Barium enema	17
Barium meal	12
Rectoscopy	5
Plain radiography	2

Table 3 *Information concerning specialty involvement from hospital records of 70 patients*

	Specialist referrals	
	Prior to enlistment (%)	Subsequent to enlistment (%)
Gynaecology	52	22
Orthopaedics	21	18
Psychiatry	10	4
General surgery	21	16
General medicine	–	23
Pain clinic	–	3
Urology	1	4
Neurology	–	4
Other	5	6

(W.H.F.T.) suggests that one such case may be expected in approximately 100 general surgical referrals, although having no outpatient disease index the authors are unable to provide greater precision. The number in the present series, however, has been inflated by secondary referrals from gynaecological and other colleagues knowing our interest.

Table 5 *Cause of death in four patients*

Patient no.	Sex	Age at death (years)	Cause of death	Time after initial referral (years)
10	F	25	Marfan's disease Pneumonia	4
11	F	79	No record of cause*	10
12	F	49	Disseminated endometrial carcinoma	0·5
13	F	66	Disseminated ovarian carcinoma	2

*Died 10 years after enlistment, 5 years after which the patient underwent sigmoid colectomy for diverticulitis

Several explanations of Carnett's test have been suggested[3,4] and the authors are unable to comment further. A few patients gave a clear causative history, for instance stumbling while burdened by a heavy weight, but most did not. The aim of the study, however, was not to find the reason for the phenomenon of abdominal wall tenderness but to determine its reliability in predicting intra-abdominal innocence, and so its potential for safely saving the cost, inconvenience and occasional misadventure of investigation.

Review of the subsequent medical experience of the 68 surviving patients supports the belief that the test has a place. Incomplete review in 14 patients undoubtedly weakens the study but we do not, anyway, claim the sign to be infallible. Like any other signs it should be interpreted in context and, as long as the clinician remains alert and does not stray from the principle of considered and careful history-taking and examination, increasing familiarity with and use of Carnett's test may render the expense and occasional danger of much investigation – and the hazard of negative laparotomy – unnecessary in the patient with chronic non-specific abdominal pain.

Table 4 *Major diagnostic events after enlistment in study*

Patient no.	Sex	Age at enlistment (years)	Subsequent diagnosis	Time after initial referral (years)	Continuing pain
1	F	48	Appendicitis Appendicectomy	2	No
2	F	52	Proctitis	7	Yes
3	F	41	Diverticulitis Pyloric ulcer Acute disc protrusion	2 3 4	Yes No No
4	F	72	Diverticulitis Rectovaginal fistula Sigmoid colectomy	7	No
5	F	57	Ulcerative colitis Spinal trauma Asthma/angina	3 4 4	Yes No No
6	F	17	Renal failure due to pyelonephritis	2	No
7	F	71	Gastric ulcer	0·5	Yes
8	F	27	Multiple sclerosis	2	No
9	F	52	Breast cancer	2	Yes

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Short note

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Horizontal testis with a varicocele: a new physical sign

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The recognition that impaired fertility might be associated with varicoceles has led to an increased interest in the condition with patients being referred at an earlier age. More patients are being seen in the first and second decades of life despite a peak incidence of varicoceles between 20 and 30 years.

Patients and methods

Twelve boys aged between 5 and 17 (mean 10) years presenting during 1989 with a varicocele were examined to determine the lie of their testes. In eight (67 per cent) of the patients the presenting complaint was scrotal swelling, and it was a dragging sensation in the scrotum in the other four (33 per cent) All patients had an intravenous pyelogram or renal ultrasound to exclude any renal pathology, no abnormalities were found.

Results

All the varicoceles were unilateral, 11 were left-sided and one was right-sided. In each patient the associated testis lay in the horizontal axis, while the unaffected testis lay in the vertical axis In nine (75 per cent) patients the affected testis was thought to be of the same size as the contralateral testis. In three (25 per cent) patients the affected testis was smaller (*Table 1*)

Table 1 *Patient characteristics*

Age (years)	Side of varicocele	Size of testes
7	Left	Equal
17	Right*	Equal
5	Left	Left smaller
15	Left	Equal
9	Left	Left smaller
8	Left	Equal
10	Left	Equal
6	Left	Left smaller
15	Left	Equal
11	Left	Equal
11	Left	Equal
12	Left	Equal

*This is the only right-sided varicocele seen in over 25 years' clinical experience

Discussion

The observation that the testis lies horizontally when associated with a varicocele has not previously been reported. It is difficult to know whether the horizontal lie of the testis with a varicocele is primary or secondary. The aetiology of a varicocele is unknown but it may be related to the perpendicular entry of the left spermatic vein into a high pressure renal venous system[1] compounded by the absence of venous valves[2].

It would seem plausible that the abnormal lie of the testis in the horizontal axis is due to the gravitational weight of the distended veins at the superior pole which displaces the inferior pole posteriorly However, a case could be made for the horizontal lie being a primary phenomenon, if the anatomy of the venous drainage emerging from the testis in varicocele was sufficiently abnormal to influence the testicular lie It would be necessary to perform further anatomical studies to resolve this matter.

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Cytoreductive surgery in disseminated non-seminomatous germ cell tumours of testis

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Between 1977 and 1988, 67 patients underwent surgical removal of residual metastatic deposits following an aggressive chemotherapy regimen (cisplatin, vincristine, methotrexate and bleomycin alternating with etoposide, actinomycin D and cyclophosphamide) for disseminated germ cell tumours of the testis (stage IIB or above). Ninety-one surgical procedures were performed. There were 63 (69 per cent) retroperitoneal lymph node dissections, 16 (18 per cent) thoracotomies, three (3 per cent) hepatic resections, three (3 per cent) craniotomies, five (5 per cent) delayed orchidectomies and one anterolateral decompression of the vertebral column. Nine (13 per cent) patients required a repeat retroperitoneal node dissection and one patient needed a repeat thoracotomy to remove recurrent metastatic deposits during the period of follow-up. Multivisceral resections and vascular reconstruction procedures were required in 20 (30 per cent) patients undergoing retroperitoneal node dissection. Fifty-five (82 per cent) patients remain in complete remission with a mean follow-up period of 49·6 months (range 2–121 months). Nine (13 per cent) patients died with metastatic disease between 2 months to 4 years after operation. There were three deaths in the perioperative period (4 per cent). The histology of the resected metastases revealed undifferentiated active tumour in 20 (30 per cent) patients, differentiated mature teratoma in 29 (43 per cent) patients and fibrosis/necrosis in 18 (27 per cent) patients. Twelve (60 per cent) patients with undifferentiated elements and 15 patients (60 per cent) with raised preoperative tumour markers (poor prognostic categories) are in complete remission. Cytoreductive surgery in patients with metastatic germ cell tumours offers the best chance of remission following chemotherapy even in poor prognostic group categories.

The introduction of sequential combination chemotherapy has dramatically improved the survival of patients with metastatic germ cell tumours of the testis[1–7]. After chemotherapy, however, residual disease may be evident clinically or radiologically with or without elevated levels of serum tumour markers, the β subunit of human chorionic gonadotrophin (βHCG) and/or α-fetoprotein (AFP). Surgical removal of this residual disease is the only accurate method of assessing the presence of active tumour tissue, especially when serum tumour markers have fallen below detectable levels. Presence of active tumour tissue indicates the need for subsequent chemotherapy[7–12] and removes cytotoxic-resistant tumour if present.

To avoid subsequent failure of ejaculation associated with formal retroperitoneal node dissection only the residual mass has been resected in this series[13]. This has the theoretical disadvantage of missing subclinical deposits but without excessive morbidity. Similar principles were applied to the thoracic procedures.

This study reports the surgical experience of this approach in the first 67 patients following an aggressive chemotherapy regimen[6] and assesses initial short-term survival.

Patients and methods

Between 1977 and 1988 a total of 67 patients who had received sequential chemotherapy[6] for disseminated non-seminomatous germ cell tumours of the testis at Charing Cross or Mount Vernon Hospitals underwent cytoreductive surgical procedures The mean age of the patients was 27 years (range 15–51 years) The primary diagnosis was established in 55 (82 per cent) patients by an orchidectomy, in six (9 per cent) patients by a biopsy of a metastatic deposit, and in the remaining six patients a presumptive diagnosis was based on grossly elevated levels of βHCG or AFP. Upon referral, the histology of the primary tumour was reassessed and classified using the British Testicular Tumour Panel classification (*Table 1*)

All patients were assessed by clinical examination, chest radiography, chest and abdominal computed tomography (CT) scanning and for levels of serum tumour markers (βHCG and AFP) If clinically indicated, CT scanning of the brain, abdominal arteriography, inferior venacavography and intravenous urography were also used to assess the extent and operability of the disease. Lymphangiography, initially used in the early stages of the study, was abandoned due to the superior definition of the para-aortic region using CT scanning

Clinical staging was performed using the Royal Marsden classification[14] (*Table 2*). Sixty-one patients (91 per cent) had stage IIc or above.

Chemotherapy

The chemotherapeutic regimen used was cisplatin, vincristine, methotrexate and bleomycin (POMB) alternating with etoposide (VP16-213), actinomycin D and cyclophosphamide (ACE) as described by Newlands *et al*[6] Seven patients had preoperative radiotherapy

Indications for cytoreductive surgery

Patients were considered suitable for cytoreductive surgery if they showed clinical or radiological evidence of a residual tumour mass in the retroperitoneal lymph nodes and/or chest with low serum tumour marker levels ($n = 42$, 63 per cent) (*Table 3*). Surgery was indicated

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Table 1 *Histology of the primary testicular tumour in 67 patients undergoing cytoreductive surgery between January 1977 and December 1988*

Histology	No of patients
Differentiated teratoma	1 (1)
Malignant teratoma intermediate	26 (39)
Malignant teratoma undifferentiated	25 (37)
Malignant teratoma trophoblastic	9 (13)
Seminoma	2 (3)
Diagnosis presumed	4 (6)

Values in parentheses are percentages

Table 2 *The Royal Marsden classification for malignant teratoma of the testis*

Stage	Classification	Involvement
I	MK+	No evidence of metastases Rising serum markers with no other evidence of metastases
II		Abdominal node involvement
	A	<2 cm in diameter
	B	2–5 cm in diameter
	C	>5 cm in diameter
III		Supradiaphragmatic node involvement
	M	Mediastinal
	N	Supraclavicular/cervical/axillary
	O	No abdominal lymphadenopathy
	ABC	As above
IV		Extralymphatic metastasis Lung substage
	L1	⩽3 metastases
	L2	>3 metastases (all ⩽2 cm in diameter)
	L3	>3 metastases (one or more >2 cm in diameter)
	H+	Liver metastases
	Br+	Brain metastases
	Bo+	Bone metastases

Table 3 *Indications for surgery**

	Markers elevated	Markers undetectable	Total	%
CT evidence of mass	22	42	64	96
CT normal but positive anti-AFP scan	2	0	2	3
Ultrasonographic evidence of mass	1	0	1	1
Total	25 (37)	42 (63)	67	

Values in parentheses are percentages; AFP, α-fetoprotein, CT, computed tomography. * Patients were considered suitable for cytoreductive surgery if there was radiological or clinical evidence of a mass with either undetectable tumour markers (67 per cent) or elevated tumour markers despite chemotherapy with a demonstrable reduction in tumour bulk to a plateau

when serum tumour markers remained elevated despite a demonstrable reduction in the tumour mass from serial CT scans ($n = 25$, 37 per cent). Surgical cytoreduction was considered essential in these patients because the residual tumour was assumed to contain active drug-resistant disease

Preoperative preparation

Chemotherapy was discontinued 2–3 weeks before surgical intervention to allow recovery from myelosuppression All patients had routine haematological and biochemical screening tests. Spirometry and blood gas estimation were performed before thoracic procedures Broad-spectrum antibiotics were used prophylactically for 5 days (cephalosporin and metronidazole for the abdominal and benzylpenicillin and flucloxacillin for the thoracic procedures)

Operative techniques[15]

Retroperitoneal node dissection. A long midline (or occasionally a right paramedian) incision was used. The ligament of Trietz was divided, the duodenojejunal junction was mobilized and the third part of the duodenum and the pancreatic head was lifted cephalad to expose the upper retroperitoneum. The left leaf of the small bowel mesentery was divided to the right iliac fossa, opening the lower retroperitoneum. The ascending or descending colon was mobilized and swung towards the opposite side By dividing the lumbar vessels, it was possible to mobilize the aorta and the vena cava to access any retroaortic and retrocaval extensions of the tumour.

Careful dissection was carried out in the interaortocaval groove and in the angle beneath the renal vessels, a common site of nodal disease The abdomen was closed with or without drainage, depending on the extent of the resection performed and its technical difficulty.

Metastatic deposits were frequently found to be adherent to the great vessels and in particular in the area bound by aorta, iliac vessels and the ureter with an apex at the renal vessels Adherence to the great vessels was marked in patients who had prior radiotherapy, with subsequent intense fibrosis The surgical objective was to remove palpable and visible disease and not total radical retroperitoneal dissection to avoid ejaculatory failure. Tumour bulk was not a deterrent to complete removal of the disease and *en bloc* multivisceral resections were performed wherever indicated.

Thoracic procedures The minimum amount of pulmonary tissue surrounding the tumour was removed. Thirteen of 16 (81 per cent) patients underwent wedge resections The size of the metastasis in one patient required lobectomy, and involvement of the main bronchus and pulmonary artery necessitated a pneumonectomy in another The number of metastases removed ranged from two to 18 Cryoanalgesia to the intercostal nerves was used in all thoracotomies

All patients received intraoperative chemotherapy (initially 50 mg methotrexate intravenously in the early stages of the study and more recently 100 mg/m^2 etoposide intravenously).

Follow-up

Patients were followed monthly by clinical examination, with estimation of serum tumour marker levels and CT scans 3-monthly After operation chemotherapy was given to patients with undifferentiated tumour tissue or elevation of the tumour marker levels and was continued until the tumour mass resolved or tumour marker levels fell below detectable levels. Once complete remission was achieved no further chemotherapy was given. Patients with necrosis, fibrosis or differentiated teratoma in the metastases received no chemotherapy after operation. No patient received maintenance chemotherapy[16].

Results

Ninety-one surgical procedures were performed (*Table 4*) These included 66 (73 per cent) abdominal, 16 (18 per cent)

Table 4 *Summary of 91 procedures performed over an 11-year period of cytoreductive surgery for disseminated germ cell tumour of the testis*

	No
Abdominal	
Retroperitoneal lymph node dissection	63 (69)
Solitary wedge excision of liver	2 (2)
Right hepatic lobectomy	1 (1)
Subtotal	66
Thoracic	
Unilateral wedge resections	6 (7)
Bilateral wedge resections	7 (8)
Lobectomy	1 (1)
Pneumonectomy	1 (1)
Excision of mediastinal lymph nodes	1 (1)
Subtotal	16
Neurosurgical procedures	3 (3)
Anterolateral decompression of spine	1 (1)
Delayed orchidectomies	5 (5)

Values in parentheses are percentages

thoracic, three (3 per cent) cranial and one (1 per cent) orthopaedic procedure. Five (5 per cent) patients had a delayed orchidectomy. Nine (13 per cent) patients had recurrent retroperitoneal lymph node involvement and underwent further cytoreductive surgery. Three (4 per cent) patients required combined abdominal and thoracic debulking. Retroperitoneal lymph node resection was performed first and thoracic debulking was carried out 12–14 weeks later. One patient underwent thoracic debulking twice.

Sixty-one of the 67 (91 per cent) patients presented with disseminated disease (stage IIc and above). Twenty-eight patients (42 per cent) belonged to the poor prognostic category as defined by their very high initial tumour marker levels before chemotherapy (βHCB > 50 000 units/l and/or AFP > 500 units/l)[6].

Forty-two (63 per cent) patients had a residual tumour mass with undetectable serum marker levels. In the remainder (37 per cent) the serum tumour marker levels were elevated despite aggressive chemotherapy. The residual disease in these patients was therefore considered to be drug-resistant tumour. Six (9 per cent) patients had evidence of increase of tumour size despite normalization of serum tumour marker levels. In these patients the resected specimen revealed a mature differentiated teratoma and in two patients an undifferentiated tumour. Four patients were operated on for CT abnormalities, subsequently found not be tumour but dense fibrosis.

Complications

The non-lymphatic structures removed to obtain a complete clearance are shown in *Table 5*. Despite the magnitude of the surgery the incidence of complications was low. Haemorrhage of more than two litres was encountered in six abdominal and one thoracic procedure. Adherence of tumour to the major vessels was the cause of bleeding in all abdominal procedures. Five (7 per cent) patients had minor complications which settled quickly without long-term sequelae. The major postoperative and long-term complications are listed in *Table 6*.

Nine patients received preoperative radiotherapy. Five of these patients have died of the disease while four patients had serious postoperative sepsis. Three patients died in the postoperative period giving an operative mortality rate of 4 per cent. The first patient was severely myelosuppressed and succumbed to a staphylococcal pneumonia and pyothorax. The second patient had an extensive tumour eroding into a friable aortic wall. The haemorrhage that resulted while dissecting this mass was uncontrollable. The third patient had extensive retroperitoneal disease requiring resection of the third and fourth part of duodenum. The patient subsequently developed a subphrenic abscess and died from a delayed haemorrhage from the aorta.

Of the 64 patients who survived the operative procedure 61 (95 per cent) were discharged within 15 days, two patients (3 per cent) between 16 and 30 days and one patient was discharged at 42 days. Inhospital stay was more prolonged for patients undergoing thoracic procedures.

Table 5 *Associated major viscera resected during cytoreductive surgery for disseminated germ cell tumour of the testis*

Structures removed*	No. of procedures ($n = 66$)
Aortic wall	4 (6)
Kidneys	4 (6)
Vertebral bodies	3 (5)
Iliac vessel wall	2 (3)
Ureter	2 (3)
Inferior vena cava	1 (2)
Right lobe of liver	1 (2)
Spleen	1 (2)
Small bowel mesentery	1 (2)
Third and fourth part of duodenum	1 (2)

Values in parentheses are percentages; * all procedures were abdominal

Table 6 *Postoperative and long-term complications of cytoreductive surgery for germ cell tumour of the testis*

Complication	No. of patients ($n = 67$)
Postoperative	
Staphylococcal pneumonia and pyothorax	1 (1)
Subphrenic abscess	1 (1)
Anastomotic stricture of ureter	2 (3)
Long-term	
Tuberculosis	3 (4)
Acute myeloid leukaemia	1 (1)
Cytomegalovirus hepatitis	1 (1)
Encephalitis	1 (1)
Total	10* (15)

Values in parentheses are percentages. Five patients had minor complications which settled with conservative management

Follow-up

Fifty-five patients (82 per cent) remain in complete remission with a mean follow-up of 49·6 months (range 2–121 months). Nine (13 per cent) patients relapsed within 2 months to 4 years after cytoreductive surgery and died with uncontrollable disease. The death of these patients was attributed to disseminated resistant disease rather than to local recurrence.

Histology of resected tumour and subsequent survival

Twenty (30 per cent) patients had undifferentiated teratoma, 29 (43 per cent) patients had differentiated teratoma and 18 (27 per cent) patients had necrosis and/or fibrosis.

Eight of the 20 (40 per cent) patients with undifferentiated teratoma died subsequently from the disease. In contrast 26 of 29 (90 per cent) patients who had differentiated teratoma remain in complete remission while 17 out of 18 (94 per cent) patients with necrosis and/or fibrous tissue are alive and in complete remission Of a total of 41 patients with stage III and IV disease at presentation, 35 (85 per cent) remain in complete remission. Twenty-five of the 28 (89 per cent) patients with high preoperative levels of tumour (poor prognosis) markers also remain in complete remission.

Eight patients in whom the markers remained elevated after surgery died from progressive disease. The remaining 15 (65 per cent) patients remain in complete remission. One patient with undetectable serum markers developed pulmonary metastases following a retroperitoneal lymph node resection and died from progressive disease. Seven (17 per cent) patients with undetectable tumour markers had histological evidence of active tumour tissue in the metastases. The remaining patients in this group remain in complete remission

Discussion

Since the description of retroperitoneal dissection by Jamieson and Dobson in 1910[17] and Hinman in 1935[18], this procedure has been used to stage testicular tumours accurately. Li *et al.* introduced cytoreductive combination chemotherapy for testicular germ cell tumours in 1960[19]. New cytoreductive agents, cisplatin and etoposide, were used in the initial treatment of patients with testicular tumours in 1977[1]. This has transformed the control of metastatic disease[6]. The histological nature of the residual masses persisting after chemotherapy, however, cannot be assessed accurately without surgery and is of important prognostic significance[20–23].

Despite the advanced stage of disease upon presentation, good complete remission can be obtained with this approach. Eighty-five per cent of patients with stage III or IV disease remain in complete remission. Fifteen (65 per cent) of the 23 patients with elevated tumour markers and 12 (60 per cent) of the 20 patients with undifferentiated tumour on histology (both poor prognostic categories[24]) remain in complete remission.

Previous surgery and 'unresectable' or incompletely resected metastases in patients treated elsewhere were not a bar to subsequent successful removal of tumour and complete remission. Multiple procedures (especially retroperitoneal node dissections) were also performed to resect recurrent metastases with subsequent complete remission in many cases. This high reoperation rate (13 per cent) may reflect the lack of formal dissection but this did not appear to compromise overall survival.

Bulk of tumour was no deterrent to a successful outcome although this required multivisceral resections as well as major vascular reconstructive procedures in some cases. In general, however, the patients were young and tolerated such procedures remarkably well. The 4 per cent operative mortality rate was higher than in other series, perhaps reflecting the advanced stage of disease[25]. The authors feel that this type of surgery must be performed only in specialist units with experience in this field with full intensive care and specialist expertise freely available.

Radiotherapy before surgery was a positive disadvantage in terms of both ultimate survival and operative technical difficulties. None of these patients derived any objective remission from this treatment. This was due to the loss of planes of dissection normally found between the great vessels and the nodal masses being destroyed by fibrosis and radiotherapy change. Consequently the removal of residual tumour tissue was always incomplete and technically very difficult and dangerous. Subsequent poor healing and a high incidence of sepsis were also noted in four out of nine (44 per cent) patients. Five (56 per cent) of these nine patients have subsequently died from metastatic disease.

This series confirms that high levels of tumour markers before operation are of poor prognostic significance[6,24] while elevated serum tumour markers after surgery reflect residual disease. We confirm that undetectable tumour markers do not rule out the presence of active disease[20].

At present POMB/ACE chemotherapy[6] remains the treatment of choice for patients with germ cell tumours of the testis. The resected tissue contained necrotic or fibrotic material in 27 per cent of patients and a further 30 per cent had active tumour, some of whom achieved complete remission after additional chemotherapy. Although full para-aortic lymphadenectomy provides a pathological staging and treatment there is substantial morbidity due to infertility Cytoreductive surgery with nerve sparing can decrease the incidence of ejaculatory failure while providing the same information and salvage rates in patients with residual active tumour[26]. We await long-term data regarding infertility in this series, but have found no detriment to survival compared with other workers[26].

Removal of retroperitoneal masses for metastatic germ cell tumours is a specialized procedure, requiring experience. Worthwhile results can be achieved with acceptable complication rates and complete remissions can be obtained in patients with advanced disease.

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Major trauma: a district general hospital experience

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A retrospective review of all patients with major trauma admitted to a busy suburban district hospital was conducted over a 1-year period. Outcome for each patient was assessed using the TRISS system which calculates the probability of survival based on anatomical extent of injury and degree of physiological disturbance at the time of admission. Thirty-nine patients were admitted following major trauma, of whom nine died. Seven of the deaths were in patients with a greater than 50 per cent chance of survival according to the TRISS system. In contrast, four patients survived who had a greater than 50 per cent chance of death. Details of these 11 cases are given. The numbers of patients who were referred to neurosurgeons and cardiothoracic surgeons in regional specialist centres were recorded, as was the relative contribution of general and orthopaedic surgeons in our own hospital. We conclude that, in the absence of specialized trauma centres, a reasonable standard of care for patients who have sustained major trauma can be delivered in a district general hospital.

Audit evaluates the effectiveness of medical practice, and has been given more prominence by the recent government white paper 'Working for Patients'[1]. The Royal College of Surgeons of England's Working Party on Trauma concluded that all is not well with the management of trauma, which is the main cause of death in people under the age of 35 years in this country Over half a million patients annually require inpatient care following injury[2].

At present in this country most patients who have sustained major trauma are taken by ambulance to the nearest accident and emergency department regardless of the other facilities available in the hospital The Royal College's report on trauma recommended that patients with life-threatening injuries should be treated in designated trauma centres. The authors were concerned about the current level of care for trauma victims in this country, particularly in district general hospitals. They cited the work by Spence *et al.*[3] comparing a small suburban hospital with a major teaching hospital. In Spence's study the small hospital was not a district general hospital, but a unit with only orthopaedics and ear, nose and throat specialists on site, with no general surgeons, intensity therapy unit (ITU) or blood bank Therefore the Royal College of Surgeons' Working Party on Trauma had no direct evidence that the level of trauma care in district general hospitals was worse than in major teaching centres. The ongoing Major Trauma Outcome Study described in the report should provide more information on the level of trauma care across the country in both teaching and district hospitals. However, the staff in these units are aware that a prospective audit of their performance is in progress, and this may alter the level of care provided.

We felt that an independent study of the treatment of patients would be valuable to ascertain the level of trauma care in a district general hospital with no input from dedicated traumatologists. The outcome of patients with major injuries treated in this district general hospital could be compared with the outcome which would be predicted if patients with the same injuries were treated in major American trauma centres by use of the TRISS index (*see* Patients and methods). Therefore, a retrospective survey was carried out encompassing all patients with major trauma admitted to a district general hospital over a 1-year period. The aim was to determine the number of patients admitted with major trauma, to monitor their treatment, and to compare each patient's outcome with their probability of survival as determined by the TRISS index which is based on outcome following treatment in a major American trauma centre.

Patients and methods

North Middlesex Hospital is a district general hospital in north London. There is 24 h on-site cover at registrar/senior registrar level in general surgery, orthopaedic surgery, anaesthetics and intensive care, and 24 h availability of radiology and laboratory services including the blood bank.

Following trauma, it is usual practice to refer patients who require specialist treatment in thoracic surgery, plastic surgery or neurosurgery to regional centres directly from the accident department after resuscitation. Approximately 90000 patients attend the accident and emergency department every year

The accident department's register and notes were used to identify all patients who might have sustained major trauma who were admitted between 1 November 1987 and 31 October 1988. The inpatient notes of this group of patients were studied to determine the exact injuries each person had sustained and the Abbreviated Injury Scale was used to calculate the Injury Severity Score (ISS) for each one[4–6].

The Abbreviated Injury Scale is a standardized way of measuring injury severity Using this scale the body is divided into seven regions (external, head and face, neck, thorax, abdomen and pelvic contents, spine, and extremities and bony pelvis). Each anatomical injury receives a score from 1 (trivial) to 6 (uniformly fatal) The ISS is derived by taking the three highest scores from different body regions, squaring each and adding them together The ISS can be related to the probability of the patient dying[5] The maximum possible ISS is 75, any patient with any injury scoring 6 is automatically given a score of 75 In this study all trauma victims with an ISS of 9 or over were included; an ISS of 9 equates to a risk of death of 5 per cent[7]

Revised Trauma Score

For each patient the Revised Trauma Score (RTS)[8] was also calculated from the notes. The RTS is derived from the Glasgow Coma Scale, the systolic blood pressure and the respiratory rate at the time of admission. Champion's most recent version of the RTS was used, since this is considered to be more accurate than previously calculated trauma scores, particularly in patients with head injuries[9] In patients in whom the respiratory rate had not been recorded on admission, a normal

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value was assumed. Sufficient data were available to record the systolic blood pressure and Glasgow Coma Scale in all patients The RTS gives a measure of the degree of physiological disturbance of the patient at the time of arrival in hospital It ranges from 7·84 (normal) to 0 (no respiratory effort, no measurable blood pressure, unconscious) It is related not only to the severity of injury but also to the delay between injury and arrival in hospital.

TRISS index

This index uses the Injury Severity Score and Revised Trauma Score to determine the probability of survival for an individual patient[10] This is achieved by comparing the ISS and RTS with a large group of pooled data obtained from thousands of trauma patients treated in American trauma centres whose outcome was known In this way the results of trauma care for patients in our study could be compared with results which would be anticipated if our patients had been treated in such a trauma centre The TRISS index has a weighting factor for patients over 55 years of age (a fixed rather than an age-related weighting), since older patients do less well following trauma There is also a weighting factor to take account of whether the injury was penetrating or blunt, for a given injury blunt trauma has a worse outcome[10]

For each patient RTS, ISS and TRISS index of survival probability were calculated. Progress of the patient including admission to ITU, surgical procedures, and transfer to any specialist centre was recorded Probability of survival was compared with actual outcome for each patient Patients with a greater than 50 per cent chance of survival who died, and patients with a greater than 50 per cent chance of death who lived, were identified as 'anomalous deaths' and 'anomalous survivors' respectively Notes of patients in these two groups were selected for closer assessment

Results

Thirty-nine patients with an ISS of 9 or over were admitted during the study period, giving an incidence of major trauma of approximately 1 in 2000 patients attending the accident and emergency department. Accident department notes and inpatient notes were found for all of these 39 patients One further patient who might have sustained major trauma was recorded in the accident register but no notes could be traced on him The patients' ages ranged from 9 to 80 years (mean 37 years); 32 of the 39 patients were male. The TRISS index for each patient is shown in *Figure 1*, the patients are separated into two groups by age since the American experience has shown that there is a higher risk of death for a given degree of injury in patients over 55 years. In this series there were 30 patients under 55 years of whom four died (13 per cent), and nine over 55 years of whom five died (55 per cent).

A third of the injuries were penetrating, mainly from stab wounds. Of the 26 blunt injuries, 17 were related to road traffic accidents and most of the rest were caused by suicide attempts involving jumping from a height or in front of a train. Most patients were managed by general surgeons (23 of 39) or jointly by general and orthopaedic surgeons (11 of 39) Only five patients were managed exclusively by orthopaedic surgeons. The distribution of the types of injury is shown in *Figure 2*. All patients were initially assessed and resuscitated in the accident department resuscitation room. Thirty of the patients were treated in the intensive care unit The distribution of surgical procedures among the trauma patients is shown in *Figure 3*.

'Anomalous deaths'

Seven patients who died had a greater than 50 per cent chance of survival calculated by the TRISS scoring system Two of these were young men with severe head injuries who died of primary brain injury despite aggressive resuscitation and transfer to a regional neurosurgical centre direct from the resuscitation room Their survival probabilities were 54 per cent and 56 per cent. Two others were men of 65 and 80 years with head injuries and multiple fractures. Their survival probabilities were 65 per cent and 81 per cent respectively (there is no weighting in the TRISS system for increasing age beyond 55 years). On admission one was hemiplegic and markedly confused, the other could only localize painful stimuli. One had a frontal skull fracture, the other a base of skull fracture Computed tomographic scan showed cerebral atrophy in both. No significant neurological improvement occurred in 3 weeks and in each case active treatment was withdrawn leading to death from bronchopneumonia. Post-mortem examinations confirmed the nature of the injuries.

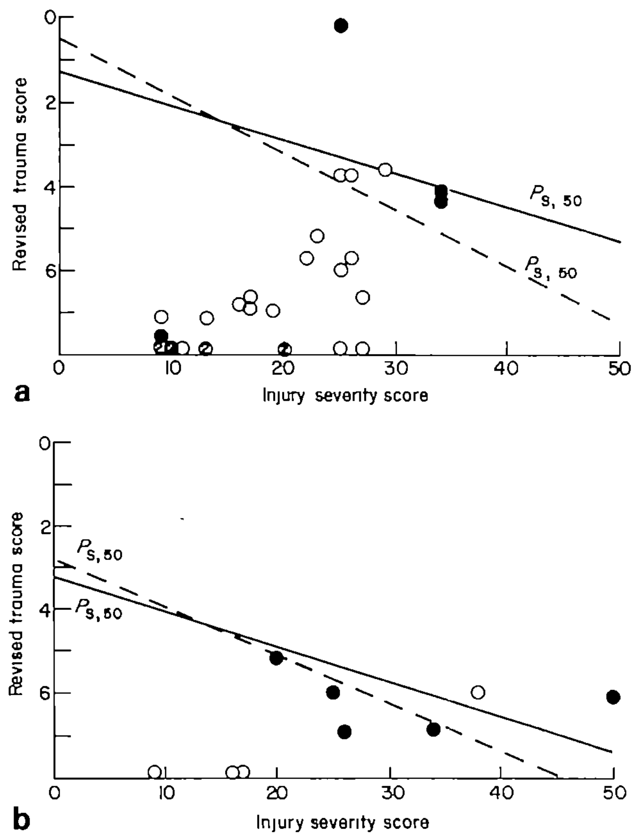

Figure 1 *TRISS indices* **a** *in patients under 55 years of age and* **b** *in patients aged over 55 years,* ○, *survivor;* ●, *death,* ——, *blunt trauma,* ---, *penetrating trauma.* $P_{s,50}$, *probability of survival of 50 per cent*

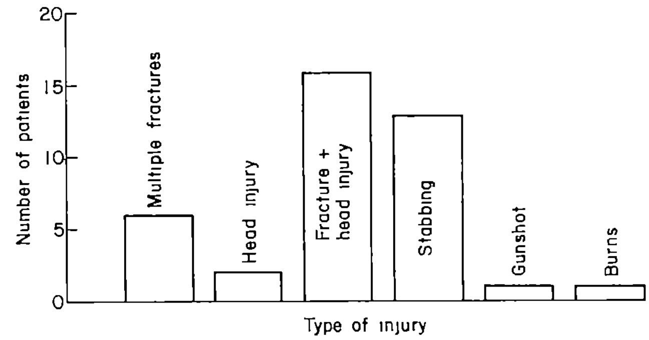

Figure 2 *Patients with major trauma nature of injuries*

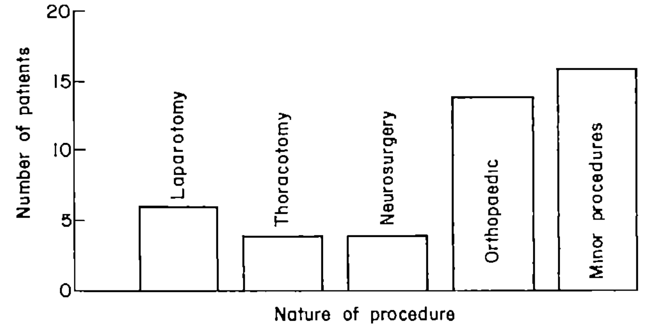

Figure 3 *Patients with major trauma surgical procedures*

A young man developed postcardiotomy psychosis 2 months after a valve replacement. He jumped from a second floor window, sustaining a fractured pelvis and bilateral calcaneal fractures. He was on warfarin at the time. He was admitted to the intensive care unit for fluid replacement, cardiac monitoring and coagulation control, but developed a pericardial effusion and arrhythmia the following day. He was referred to the regional cardiac surgery unit (where he had had his original operation), transferred that day, and was taken to theatre for open pericardial drainage, but died of an arrhythmia during this procedure His probability of survival was 99 per cent by the TRISS scoring system, but undoubtedly his cardiac condition and anticoagulation at the time of injury contributed significantly to his death.

A further anomalous death was thought to be due to late presentation after injury. A psychiatric patient presented 36 h after falling and sustaining multiple rib fractures with a haemothorax and a flail segment, a fractured humerus and fractured pubic rami She had initially been treated elsewhere and was then referred to us. On arrival she was cyanosed and hypovolaemic. A chest drain was already in place. She was resuscitated and ventilated in the intensive care unit but died shortly afterwards. Her probability of survival was calculated as 56 per cent; earlier intensive treatment might have changed the outcome.

The final anomalous death occurred in a 65-year-old man from a road traffic accident who had sustained a head injury with temporary loss of consciousness, a flail chest with haemothorax, and a fractured femur, clavicle and pubic rami His calculated probability of survival was 68 per cent. He was admitted immediately to the intensive care unit, a chest drain was inserted and he was ventilated. He developed adult respiratory distress syndrome which gradually resolved, but he could not be weaned from the ventilator. Acute renal failure was successfully treated by peritoneal dialysis, but 3 weeks after admission he deteriorated, developed jaundice and refractory hypotension and died several days later. There had been some delay between his accident and his arrival in hospital since he had had to be cut free from the vehicle in which he had been travelling. It is possible that earlier fluid replacement and ventilatory support might have led to his survival.

'Anomalous survivors'

There were four patients who survived whose calculated risk of death was greater than 50 per cent. The first was an 18-year-old with a severe head injury. On arrival he had one fixed dilated pupil and a flexion response to pain. He also had fractured pubic rami. After initial resuscitation, intubation and ventilation he was transferred to a neurosurgical unit where a computed tomographic scan showed bilateral frontal contusions. He was immediately returned to our hospital where he recovered slowly, initially in the intensive care unit He was discharged home after 3 months but had a persistent personality change and was not self-caring. His probability of survival was 48 per cent.

A 64-year-old man fell from a height while drunk and suffered an extensive compound parietal skull fracture, a fractured radius and a pulmonary contusion. On arrival he was hemiplegic with a fixed dilated pupil. He was resuscitated, intubated, ventilated and transferred to a neurosurgical unit where he underwent debridement of a compound skull fracture. After a week he was returned to our hospital. A year later he was still on the general surgical ward, hemiplegic, dysphasic and doubly incontinent. His survival probability was 41 per cent

A man was admitted following an abdominal gunshot wound. He was barely conscious with impalpable pulse and blood pressure. Perforated small bowel was protruding from his abdominal wound. Urgent resuscitation restored a pulse of 100 and blood pressure of 120 Laparotomy was carried out 45 min after his arrival The abdomen contained more than 3 litres of free blood, with multiple small and large bowel perforations and gross faecal contamination. The damaged small bowel was resected and anastomosed. The perforated large bowel was resected and a defunctioning colostomy brought out The wounds were left open. He was transfused a total of 12 units of blood. He made a good recovery and his stoma was later taken down. His probability of survival was 45 per cent.

The fourth anomalous survivor was a young man with a cardiac stab wound. He arrived with a pulse of 40 and an unrecordable blood pressure. Urgent resuscitation was undertaken and he was in theatre within 20 min of arrival in hospital. A thoracotomy was performed and a laceration in the right ventricle was repaired. He made a good recovery but has a persistent ventricular septal defect, indicating that the original wound had passed through the cardiac septum. His calculated survival probability was 41 per cent.

It was felt that the good results in these latter two cases could be attributed to the early aggressive surgical intervention which they received. Neither would have been likely to survive transfer to a specialist centre despite full resuscitation

Referrals to regional specialist centres

Ten patients were referred from the resuscitation room to one of two neurosurgical units. Computed tomographic scan showed a compound depressed skull fracture in three, all of whom were operated on. One patient had an extradural haematoma which did not require surgery, three had primary brain injury (all were returned immediately to our hospital) and two had cerebral atrophy only Only one scan in a transferred patient was completely normal. One patient had a computed tomographic scan at our hospital (scanner only staffed from 09.00 to 17.00 hours; the scan showed a cerebral contusion and after discussion with the neurosurgeons the patient remained at our hospital. No neurosurgical procedures were carried out at the North Middlesex Hospital. Five of the nine patients transferred with head injuries were intubated and ventilated before transfer.

Four patients required thoracotomy. Two of these procedures were carried out at regional centres on patients considered stable enough for transfer after resuscitation. One other was one of the 'anomalous' survivors described above. The fourth, whose survival probability was 1 per cent according to the TRISS index, was operated on at the North Middlesex Hospital by a cardiothoracic surgeon who came out from the regional unit. This patient died in theatre.

One patient was referred to the regional plastic surgery unit. This elderly man had sustained 40 per cent full thickness burns and smoke inhalation. He was resuscitated, intubated and ventilated before transfer. His survival probability was 25 per cent. He died 2 days after admission

Discussion

This study shows the incidence of major trauma and the distribution of types of injury found in patients attending a busy district general hospital. Although the study was carried out retrospectively, notes were found for all but one of the patients admitted who may have sustained major trauma. However, in six cases inadequate data recording at the time of admission meant that an accurate RTS could not be determined. In five of these cases the respiratory rate had not been recorded, and in the sixth there was inadequate information to accurately determine the Glasgow Coma Scale. In these cases the highest (least deranged) score compatible with the available information was assigned ISS is recorded retrospectively since it reflects the anatomical extent of injury. Therefore all information in the notes including radiograph reports, operation notes and post-mortem reports was available for the calculation of ISS.

The results show a higher degree of general surgical involvement and a higher proportion of penetrating wounds than is usually described in this country[11]. This may reflect an increase in violent crime, and other recent studies support this hypothesis[12,13].

The TRISS system is the 'gold standard' for assessing outcome in major trauma audit. This system gives a calculation of the probability of survival for each patient after major trauma based on the standard of care delivered in American trauma centres. The highlighting of so-called 'anomalous survivors' and 'anomalous deaths' is a statistically inaccurate concept, but has been used to enable comparison between our results and those described in the paper by Spence *et al.*[3]. Statistically a 50 per cent survival probability means exactly that, and if one took a 60 per cent survival probability as the cut-off point then four of every ten patients at this level would be expected to die. In our series there were seven 'anomalous deaths' including two patients from whom active treatment was withdrawn. There were four 'anomalous survivors' but two of these were left with severe residual handicap. In these 11 cases the survival probability was between 40 per cent and 60 per cent for each patient, and their recording as 'anomalous' results may not be significant The overall distribution of results of our patients does not deviate far from what would be expected if the patients had been treated in a trauma centre.

The Royal College of Surgeons' report on trauma suggests that patients whose ISS is greater than 20 should be referred to a trauma centre. In their evidence they include the paper by Spence *et al.*[3] in which major trauma is defined by an ISS of over 16. However, it is often not possible to determine the ISS accurately at the scene of the accident, or even rapidly after admission to the resuscitation room, since the score is based on the anatomical extent of the injuries. Diagnostic procedures are necessary to obtain an accurate ISS. Indeed, the very patients who usually represent 'anomalous deaths' are those with unrecognized injuries such as ruptured spleen or extradural haematoma[14,15] Ruptured spleen alone represents an ISS of 9. This point is well made by Eastman *et al* [7], and it was for this reason that we set an ISS of 9 as our threshold for defining major trauma.

In order to avoid anomalous deaths two things are necessary. First, a system for defining which patients are seriously injured must be accurate and easy to use for those attending the scene of the accident, i.e. the ambulance personnel. Second, all patients who may be at significant risk of death should be treated by experienced trauma surgeons. Since this study was undertaken a trauma team has been introduced at the North Middlesex Hospital. In any case where the ambulance personnel think that a patient has suffered major trauma they alert the hospital before arrival. The surgical, anaesthetic and orthopaedic registrars on call are 'crash-bleeped' to the resuscitation room to await the arrival of the patient. The anaesthetic input is felt to be particularly important so that early intubation and ventilation may be carried out for patients with serious head injuries or multiple injuries. Even if patients are to be referred on elsewhere, resuscitation and diagnostic manoeuvres (such as chest drainage and peritoneal lavage) are essential so that the patient is stable before transfer.

It is important to avoid unnecessary referrals to regional centres because of the paucity of intensive care beds available in such units. North Middlesex Hospital is fortunate in that there are two regional centres at nearby teaching hospitals for both neurosurgery and cardiothoracic surgery. Frequently when an emergency referral is made from our hospital one or other of these centres has been unable to accept the patient because of lack of an intensive care bed. This prolongs the time before the patient can be transferred Any regional trauma centre wishing to take over major trauma care would need a number of dedicated intensive care beds

Improvements in trauma care may be possible without the introduction of trauma centres. There is a growing awareness of the possibility for improving trauma care, and measures such as the introduction of trauma teams may lead to such an improvement. Increasing numbers of doctors involved in the care of patients with major injuries are attending Advanced Trauma Life Support courses[15], and this should also lead to an improvement in the standard of trauma care. There is a continuing trauma audit in progress in the UK at present (Major Trauma Outcome Survey, Spence *et al.*[3]), and it is hoped that both teaching and district hospitals will show improved results for patients who have sustained major trauma.

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Long-term survival in patients operated on for benign peptic ulcer disease

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Survival rate was analysed in a cohort of 6459 patients who had undergone partial gastrectomy for benign ulcer disease and who had survived the first year after operation. The cohort was followed for 27–35 years. There was a slight but significant decrease in relative survival rate to 92 per cent (95 per cent confidence interval 87–97 per cent) 35 years after operation. No decrease in relative survival rate was observed during the first 20 years after operation. There was no difference by gender or surgical procedure, but patients operated on for gastric ulcer, compared with duodenal ulcer, and patients operated on at younger ages had a poorer relative survival rate. The effects of partial gastrectomy on survival, both overall and by diagnosis or age at operation, are probably attributable to confounding factors linked with the peptic ulcer disease rather than to the surgical procedure itself. We conclude that partial gastrectomy seems to have very little impact on survival once the patient has survived the first year after operation.

Since 1882, when the first partial gastrectomy for ulcer disease was performed[1], this operation has been carried out widely in the treatment of gastric and duodenal ulcer. In Sweden, partial gastrectomy remained the standard surgical treatment until the early 1970s, when parietal cell vagotomy was introduced, mainly for the surgical treatment of duodenal ulcer Partial gastrectomy was the most common major operation in Swedish hospitals during the 1950s.

The mortality rate among patients who have undergone partial gastrectomy has been analysed in several studies. There are reports on increased mortality from tuberculosis[2,3], different forms of cancer[4–7], suicide[2,3,8], ischaemic heart disease[9], respiratory diseases[9,10], hepatic cirrhosis[7,8] and cerebrovascular diseases[10]. By contrast, there have been only two survival analyses[7,10] and both have shown a decreased survival rate. It has been debated whether the operation in itself has long-term detrimental effects on health or whether decreased survival rates and higher mortality rates are caused by other patient characteristics linked to the peptic ulcer disease. Since survival rates have only been sparsely investigated, it has not been established how great these effects are. The aim of this study was to analyse the relative survival rate in a population-based cohort of 6459 patients who had undergone partial gastrectomy for benign ulcer disease in the years 1950–1958.

Patients and methods

Source population

The source population consisted of residents in five counties within the Uppsala health care region with a total population of about 1 2 million in 1955 There were 20 surgical departments in this area during the 1950s There was no private care for ulcer patients who were considered for operation in the region One of the authors (G.L) visited these departments and searched the surgical records to identify all patients who had undergone partial gastrectomy for ulcer disease from 1950 to 1958 This search yielded 7138 patients.

The cohort

Of the 7138 patients, 679 were excluded because of a missing or incorrect national registration number (which was necessary for exclusive identification of the individual and for follow-up through other records) or death during the same calendar year as the operation (0–12 months after operation). After these exclusions, 6459 patients (90 per cent) remained in the final cohort. The ratio of men to women in the cohort was 5·1 Half of the patients were younger than 50 years at the time of operation, and the age distributions among men and women were similar The Billroth I procedure had been used in 1738 patients (27 per cent) and the Billroth II procedure in 4693 (73 per cent), in 28 patients the procedure was not known At the time of operation 1755 (27 per cent) patients had a diagnosis of gastric ulcer, 3947 (61 per cent) duodenal ulcer, and 757 (12 per cent) of an ulcer whose location was not stated. The classification of the ulcer was based on the diagnosis reported in the operating theatre records

Record linkages

Data for all patients were compiled in a computer file which was linked to three nationwide registries – the Death Registry, the Registry of Population Changes (emigration register) and the Swedish Population and Address Registry (with information about all living persons in Sweden). For each patient the number of years of observation until the date of death, the date of emigration or the closing date of this follow-up, 31 December 1985, was obtained

Statistical procedures

The observed survival rates for all causes of death were calculated by means of the actuarial or life-table method[11] To compare the survival rate in the cohort with that in the general population, the relative survival rate[12,13] was calculated. This is the ratio between the observed survival rate in the patient group and the expected survival rate in the general population, which was obtained from Swedish population tables by age (5-year intervals), gender and calendar year[14]

Results

At the closing date of this follow-up, 2659 patients were still alive. The observed survival rate after 35 years was 32 per cent (*Figure 1*). The relative survival was unchanged for the first 20 years after operation, after which there was a decrease (*Figure 1, Table 1*). Thirty-five years after operation the relative survival was significantly decreased by about 8 per cent (point estimate 92 per cent; 95 per cent confidence interval 87–97 per cent).

Relative survival rate was also analysed after stratification for gender, surgical procedure, diagnosis at operation and age at operation (*Table 1*). There was no difference in the relative survival rate between sexes or between patients undergoing different surgical procedures. Patients operated on for gastric ulcer had a poorer relative survival rate after 35 years

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(80 per cent) than those with duodenal ulcer (96 per cent) (*Table 1*). The age at operation also influenced the relative survival rate (*Table 1*). Younger patients had a decreased relative survival rate (88 per cent up to 39 years, 94 per cent at 40–49 years), while the relative survival rate was increased in older patients (107 per cent at 50–59 years, 106 per cent at 60–69 years).

Discussion

In this study, survival rate after partial gastrectomy for benign ulcer disease was analysed from the year of operation and compared with the expected survival rate, calculated from life-tables, in the general population It was found that the survival expectancy was unchanged during the first 20 years Thereafter the relative survival rate decreased slightly There was no difference by gender or surgical procedure, but survival rate was decreased in patients operated on for gastric ulcer compared with duodenal ulcer, and in younger patients.

The present cohort is large and population-based. Reliable estimates of the survival expectancy in the background population were available. In this cohort all patients who died within the same calendar year as the operation were excluded. Thus, patients who had died as a result of postoperative complications were excluded, and it was the survival rate after the first year after operation and on a long-term basis that was analysed. When studying patients undergoing operation for peptic ulcer disease, it has to be borne in mind that these patients are probably not representative of ulcer patients in general. Firstly, patients undergoing surgery are likely to be in better overall medical condition and this would increase the relative survival rate. This factor is probably more pronounced at older ages. Secondly, patients who have been considered for operation are more likely to have more severe ulcer disease and a higher incidence of gastric ulcer.

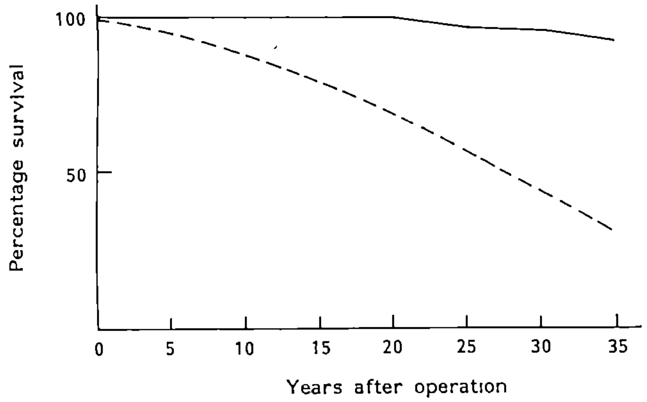

Figure 1 *Relative and observed survival for the total cohort of 6459 patients who had undergone partial gastrectomy for benign ulcer disease* ——, *Relative survival*, – – –, *observed survival*

The characteristic common to all patients in our cohort is the partial gastrectomy, but the lower relative survival rate after 20 years may not necessarily have been caused by the operation itself Other risk factors for premature death may have been over-represented in the cohort. For example, it has been reported that there are more smokers[15] and persons of low socioeconomic status[16] among patients with ulcer disease Such factors may act as confounders and influence the survival rate The mortality analyses published so far[2,4,7,9,10] indicate that this is indeed the case, as the mortality rates from disorders coupled to smoking and low socioeconomic status have been increased

The data from survival analyses also support the view that it is patient characteristics associated with the peptic ulcer disease that decrease the survival rate rather than the type of operation in itself. Stemmermann *et al*[10] followed up 8006 Hawaiian Japanese men for 10 years after a baseline examination between 1965 and 1968. The observed survival after 10 years among the 407 gastrectomy subjects was 88 per cent, which was significantly lower than the 92 per cent among the non-operated subjects. The ten-year mortality rate was higher in patients operated on for gastric ulcer compared with duodenal ulcer The number of cigarettes smoked per day and the amount of alcohol used per month were higher among patients operated on for gastric ulcer than in non-operated subjects. No such differences were found when patients operated on for duodenal ulcer were compared with non-operated patients After adjustment for age, smoking and intake of alcohol, the decrease in survival in the surgically treated group disappeared This would indicate that such factors rather than the ulcer disease itself or the operation are responsible for the increased mortality rate in gastrectomized patients and for the difference between patients with gastric and duodenal ulcer In a cohort of 779 men who underwent gastrectomy or vagotomy between 1947 and 1965, McLean Ross *et al*[7] found a decreased survival rate. There was an increased mortality rate in the three major age groups (30–39, 40–49 and 50–59 years at operation) of 14, 28 and 24 per cent compared with the general population

In the present large population-based study, the detrimental effects on survival are less pronounced than have been previously reported. The partial gastrectomy appeared to have

Table 1 *Relative survival rates by gender, surgical procedure, diagnosis and age groups*

	5 years	10 years	15 years	20 years	25 years	30 years	35 years
All	100 (99–101)	101 (100–102)	102 (100–103)	101 (99–102)	98 (96–100)	96 (93–99)	92 (87–97)
Sex							
Male	100 (100–101)	101 (100–102)	102 (100–103)	100 (99–102)	98 (95–100)	96 (92–99)	92 (87–98)
Female	101 (100–102)	101 (99–103)	102 (99–105)	101 (97–105)	98 (93–102)	98 (92–104)	92 (81–103)
Surgical procedure							
Billroth I	99 (98–101)	100 (98–102)	100 (98–103)	99 (96–103)	98 (94–102)	98 (92–103)	96 (85–108)
Billroth II	100 (100–101)	101 (100–102)	102 (101–104)	101 (99–103)	98 (95–100)	96 (93–99)	91 (86–97)
Diagnosis at operation							
Gastric ulcer	100 (98–101)	100 (98–102)	99 (97–102)	97 (93–101)	90 (85–95)	90 (84–97)	80 (68–93)
Duodenal ulcer	101 (100–101)	101 (100–102)	103 (101–104)	102 (100–104)	100 (97–102)	98 (95–101)	96 (90–101)
Age at operation (years)							
≤39	100 (99–100)	99 (99–100)	98 (97–99)	96 (94–98)	93 (91–95)	91 (89–94)	88 (84–93)
40–49	100 (100–101)	100 (99–101)	100 (99–102)	101 (99–103)	99 (97–102)	98 (94–102)	94 (85–104)
50–59	100 (99–101)	100 (99–102)	104 (101–106)	103 (100–107)	102 (97–107)	103 (95–111)	107 (84–130)
60–69	102 (99–104)	105 (101–109)	109 (103–116)	109 (99–119)	106 (90–121)	120 (87–154)	106 (0–246)

Values are given as percentage (95 per cent confidence limits) no effect on the relative survival rates during the first 20 years after operation. Thirty-five years after operation the relative survival decreased by 8 per cent. There was no difference by sex or surgical procedure. The relative survival decreased to a greater extent in patients operated on for gastric ulcer than in those with duodenal ulcer. This difference is in accordance with the findings of Stemmermann *et al.*[10] and can be explained by differences in the distribution of other risk factors.

We found that the relative survival rate was decreased in patients operated on at a younger age, whereas in older patients the observed survival rate was close to that expected. There is a possibility that patients operated on at a young age have a more aggressive ulcer disease and thus might constitute a group with a comparatively high frequency of smokers and persons of low socioeconomic status. If so, these factors might explain the decreased survival among these patients. A selection of patients in better physical and medical condition among the patients operated on at an older age is a reasonable explanation for the more favourable relative survival in higher age groups.

The effects of partial gastrectomy for ulcer disease on the relative survival rate are more likely to be attributable to confounding factors linked with the peptic ulcer disease than to the surgical procedure in itself. In this cohort the decrease in relative survival rate was low and was apparent only after long-term follow-up. The partial gastrectomy therefore seems to have very little impact on survival once the patient has survived the first year after operation. We consider that peroperative mortality and long-term morbidity are more important factors to take into account than the minor effect on the long-term mortality when the type of operation for ulcer is being decided.

Acknowledgements

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Effects of cardiac surgery and intraoperative hypothermia on energy expenditure as measured by doubly labelled water

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Total energy expenditure (TEE) was measured over two 10-day periods, before and after operation in 16 patients undergoing coronary artery surgery and randomized to have cardiopulmonary bypass with an intraoperative blood temperature of either 28 or 20°C. TEE was measured with doubly labelled water containing stable isotopes of hydrogen and oxygen to allow calculation of TEE over fixed periods from the differential rate of excretion of the two isotopes. Results were available for eight patients in the 28°C group but for only seven in the 20°C group (one patient in this group was excluded as the temperature allocated was not achieved). The groups were similar with respect to body-weight and lean body mass. The 20°C group received more grafts than the 28°C group, resulting in an increase in cross-clamp and bypass times. Mean preoperative TEE was similar in both groups. The mean difference in fractional turnover rates of hydrogen and oxygen was not significantly different in the postoperative period. There was a non-significant increase in the mean 10-day postoperative TEE, calculated in total calories, of 4·7 per cent in the 28°C and 5·1 per cent in the 20°C group. When changes in postoperative TEE were calculated according to lean body mass, the mean increases were respectively 3·7 and 3·2 per cent. Cardiac surgery utilizing cardiopulmonary bypass and intraoperative hypothermia results in only a modest increase in postoperative TEE. In this study a more profound level of intraoperative hypothermia did not influence the change in postoperative TEE.

The effect of surgical trauma on total energy expenditure (TEE) is controversial Some groups have reported little postoperative change[1,2] while others have reported variable increases of up to 25 per cent[3–7]. Cardiac surgery combines cardiopulmonary bypass and intraoperative hypothermia with conventional surgical injury. Intraoperative hypothermia during cardiac surgery modifies the endocrine[8,9] and protein turnover[10] responses to surgery, but changes in TEE after cardiac surgery have not been reported and it is not known whether intraoperative hypothermia can modify any such changes.

The doubly labelled water technique permits measurement of TEE by administration of stable isotopes of hydrogen and oxygen (^2H_2O and $H_2{}^{18}O$)[11–18] The technique is based on the observation that oxygen atoms in respired carbon dioxide are in eqilibrium with oxygen atoms in body water through the action of carbonic anhydrase[18]. After mixing with body water, ^2H is lost as water whereas ^{18}O is lost both as water and as carbon dioxide. The difference in the rate of excretion of the two isotopes from the body is therefore due to carbon dioxide production from which TEE can be calculated[11]. The technique can provide an integrated assessment of TEE over 1 day in contrast to the factorial computations of daily energy expenditure derived from short periods of indirect calorimetry.

The aims of this study were threefold· to examine the effects of uncomplicated cardiac surgery on energy expenditure; to investigate whether changes in energy expenditure could be modified with a more profound level of intraoperative hypothermia; and to determine the applicability and suitability of the doubly labelled water technique in surgical patients

Patients and methods

Protocol

Patients presented 10 days before surgery and, after passing a baseline urine sample to determine background enrichment, drank a tumbler of water containing 75 mg ^{18}O per kg body-weight (8 7 atom per cent ^{18}O, Delta Isotopes, Crewe, UK) mixed with duetenum (25 mg ^2H per kg body-weight, 99 8 atom per cent, MSD Isotopes, Montreal, Canada) Patients then went home and collected daily urine samples (20 ml) until surgery

A second identical dose of doubly labelled water was administered 6 h after surgery as an intravenous infusion after microfiltration Residual levels of oxygen and hydrogen enrichment were calculated from the presurgery isotope decay curves After surgery, 20 ml morning urine samples were collected for a further 10 days.

Patients and methods

Sixteen male patients undergoing elective coronary artery surgery were prospectively randomized to an intraoperative blood temperature of 28 or 20°C. The age range of the patients was 40–62 years and all required at least two coronary artery grafts using saphenous vein and/or internal mammary artery

No patient was unstable or in cardiac failure or known to have diabetes mellitus, hyperlipidaemia, endocrine disorders, or renal or hepatic impairment All patients were nutritionally replete, judged by typical biochemical and anthropometric parameters. Informed consent was obtained from all patients and the study was approved by the Hospital Ethical Committee.

Anaesthetic regimen

A standard anaesthetic regimen was followed, 20 mg temazepam was administered on the night before surgery, anaesthesia was induced with

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midazolam and and fentanyl, and intubation was performed after the administration of a muscle relaxing agent (atracurium or pancuronium). During surgery, anaesthesia was maintained with a combination of morphine, fentanyl and midazolam and boluses of atracurium or pancuronium. The total anaesthetic dose of morphine was <2 mg/kg body-weight and of fentanyl <20 μg/kg body-weight.

Cardiopulmonary bypass

Bypass was performed using pulsatile perfusion, bubble oxygenation, a 40 μm pore size arterial filter and 2 litres of crystalloid prime. The intraoperative blood temperature was continuously recorded in the extracorporeal circuit (Therm-A, Edwards CVS Division, Berkshire, UK) while the core temperature was simultaneously measured in the nasopharynx (Yellow Springs series 401 temperature probe, Siemens Ltd., Cumbernauld, UK). The perfusion flow rate was calculated from the formula that at normothermia full flow is equivalent to 2·4 l/m² per min. During intraoperative hypothermia the flow rate was reduced but did not fall below 1·5 l/m² per min. One litre of 4°C cardioplegic solution (St Thomas' Hospital formula) was administered in divided doses during the cross-clamp period and the heart was topically cooled with physiological saline at 4°C. Acid–base status during bypass was controlled by pH-STAT management. On the patient's return to the cardiac intensive care unit, boluses of morphine (1–2 mg), midazolam (1–2 mg) and vecuronium (2 mg) were used to maintain analgesia and permit mechanical ventilation until the patient was fully rewarmed, haemodynamically stable and ready for extubation.

^{18}O analysis

All urine samples were analysed for ^{18}O enrichment by continuous flow isotope ratio mass spectrometry (CF-IRMS)[19]. 1·5 ml samples of urine were equilibrated with carbon dioxide (18·5 ml 10 per cent carbon dioxide) in a vacutainer at 25°C for 72 h. 1 ml gas samples (100 μl carbon dioxide) were then injected into a CF-IRMS (Roboprep-CN Sample Convertor, Europa Scientific, Crewe, UK) interfaced to an MM602 IRMS (VG Isogas, Middlewich, UK) via a septum inlet where the gas was in turn dried, purified by gas chromatography and bled into the mass spectrometer. The mass ratio 46/44+45 was measured automaticaly and the instrument was calibrated against distilled water standards of known ^{18}O enrichment. The coefficient of variation for replicate urine samples was <0·1 per cent. Accuracy was within 2 ppm over the calibrated range (0–350 ppm above background).

Deuterium analysis

Baseline urine samples, samples showing maximum ^{18}O enrichment and those every second day from those samples were analysed for deuterium enrichment by conventional dual batch inlet gas source isotope ratio mass spectrometry, after reduction to hydrogen gas over depleted uranium[20].

Each sample was analysed with reference to a calibrated hydrogen working standard, and the internal precision of deuterium analysis at natural abundance was 0·05 parts per million (1 s.d.).

Calculations

Total body water was estimated by extrapolating the ^{18}O enrichment of the first five samples to zero time. At the time of surgery it was calculated in a similar fashion after calculating by extrapolation the residual isotope from the first ^{18}O dose. It was assumed that ^{18}O overestimated total body water by 1 per cent[12].

Lean body mass was calculated assuming constant hydration, assuming that lean tissue contains 73 per cent water and fat tissue contains negligible amounts[21]:

$$\text{Lean body mass} = \frac{\text{Total body water}}{0{\cdot}73}$$

Energy expenditure was calculated using the formula of Lifson and McClintock, which includes corrections for isotope fractionation[11,22].

$$r_{CO_2} = N(k_O - k_D) - 0{\cdot}015 k_D N/2(1{\cdot}04)$$

where r_{CO_2} is the number of moles of carbon dioxide per day, N is the size of the body water pool in moles, 2 is the constant equating two atoms of oxygen in each molecule of carbon dioxide with one in each molecule of water, k_O is the fractional turnover rate of oxygen, k_D is the fractional turnover rate of deuterium, and 1·04 and 0·015 are correction factors for isotopic fractionation.

Energy expenditure was calculated from Weir's formula[23], by converting moles of carbon dioxide to the volume of carbon dioxide in litres ($V_{CO_2} = r_{CO_2} \times 22{\cdot}4$). Because the doubly labelled water method provides a measure of carbon dioxide production, rather than oxygen consumption, the calculation of TEE requires some estimation of the average respiratory quotient (RQ) over the study period. Although RQ values may vary widely over short periods, mean values show little variation over longer periods[24,25] except in cases of severe energy imbalance. As in other studies using doubly labelled water, a mean RQ value of 0·85 was assumed over the study period[25]. Even in the unlikely situation of the true RQ having been 0·7 or 1·0 over the study period, this would still have produced a maximum error of ±3 per cent in TEE[25].

Statistical analysis

Statistical analysis was based on a paired *t* test to compare serial differences within the same group and an unpaired *t* test to compare differences between groups. Differences were considered statistically significant when the probability of their arising by random sampling error was less than 1 in 20 ($P<0{\cdot}05$).

Results

Results are presented in *Tables 1* and *2*.

There were eight patients in the 28°C group and seven in the 20°C group. One patient randomized to the 20°C group had only a single vessel suitable for coronary grafting at operation, and it was therefore decided to cool the blood temperature to 30°C rather than 20°C. This patient was excluded from subsequent analyses.

The groups were similar with respect to age, height, body weight (*Table 1*) and lean body mass, calculated from total body water (*Table 2*).

The 20°C group received more grafts than the 28°C group, resulting in a significant increase in the cross-clamp and bypass times in this group (*Table 1*).

The mean preoperative TEE was similar in both groups. There was a similar increase in the mean 10-day postoperative TEE, calculated in total calories, of 4·7 per cent in the 28°C and 5·1 per cent in the 20°C group ($P>0{\cdot}05$ in both groups). When changes in postoperative TEE were calculated according to lean body mass the increases were respectively 3·7 per cent and 3·2 per cent.

Discussion

Cardiac surgery utilizing cardiopulmonary bypass and hypothermia is a unique form of operative injury and widely assumed to be a major form of surgical trauma. The circulation of blood through the extracorporeal circuit results in systemic activation of inflammatory mediators such as complement and produces a state of whole-body inflammation[26]. Intraoperative hypothermia can modify the metabolic response to surgery, including some components of the acute phase response[27], the endocrine response[8,9], protein turnover and nitrogen balance[10]. Although the precise control of fuel utilization and energy expenditure in the postoperative period are not fully elucidated, the counter-regulatory hormones are strongly incriminated[28–30]. Infusion of catecholamines and cortisol in healthy volunteers can mimic some components of the metabolic response and in particular in elevation in energy expenditure[28–30]. It is feasible, therefore, that modification of the counter-regulatory hormone

Table 1 *Clinical and operative features of the two temperature groups*

	Lowest blood temperature		
	28°C	20°C	*P*
Number of patients	8	7	
Age (years)	55(2)	53(3)	n.s.
Height (cm)	175(1)	170(3)	n.s.
Weight (kg)	79(3)	76(6)	n.s.
Bypass time (min)	84(7)	103(6)	<0·05
Cross-clamp time (min)	50(4)	63(3)	<0·05
Number of grafts	2·9(0·2)	3·6(0·2)	<0·05

Values given are mean(s.d.)

Table 2 *Weight, total body water (TBW), lean body mass (LBM) and changes in energy expenditure expressed as total calories and related to LBM*

	Weight (kg)	TBW (kg)	LBM (kg)	kcal/day		kcal/kg per day		kcal/kg LBM per day	
				Preoperative	Postoperative	Preoperative	Postoperative	Preoperative	Postoperative
28°C group									
	80	39	53	1779	2153	22	27	33	40
	67	49	66	2384	2657	36	40	36	40
	78	36	49	2827	1430	36	18	57	29
	63	32	44	2080	1863	33	30	47	42
	85	45	61	2589	2965	30	35	42	49
	87	49	67	2075	2408	24	28	31	36
	86	40	55	1377	2608	16	30	25	48
	84	51	69	1973	1815	24	22	28	26
Mean	79	43	58	2135	2237	27·6	28·8	37·4	38·8
s.e.m.	3	2	3	163	182	2·6	2·4	3·8	2·9
Paired *t* test				n.s		n.s		n.s.	
20°C group									
	63	30	41	1946	1514	31	24	48	37
	100	51	70	2073	2327	21	23	30	33
	78	49	66	2024	2425	26	31	30	36
	64	34	46	2033	1789	32	28	44	39
	89	51	70	3552	3401	40	38	51	49
	82	44	61	2230	2207	27	27	37	36
	59	38	53	1913	2914	32	49	36	55
Mean	76	42	58	2253	2368	29·9	31·4	39·4	40·7
S.e.m	6	3	4	220	242	2·3	3·5	3·2	3·1
Paired *t* test				n.s		n.s.		n.s	

There was no significant difference between the groups

response with profound intraoperative hypothermia[9] would lead to modification of changes in postoperative energy expenditure. There has, however, been no previous study of alterations in energy expenditure in patients undergoing cardiac surgery or the effects of different levels of intraoperative hypothermia on any such changes.

Alterations in the metabolic rate in disease states was first described by Dubois[31] in 1924 and following trauma by Cuthbertson[32] in 1932, but there is still no consensus on the effect of surgical injury on energy expenditure, Kinney's group reported minimal changes in energy expenditure after elective surgery of moderate severity, and gradual increases in the metabolic rate with increasing severity of injury[1,2]. Other groups, however, have reported increases in postoperative energy expenditure from 10 per cent[5,6] to 25 per cent[3,4,7].

The reasons for such variations include differences in the severity of the illness, the pre-existing nutritional status of the patients, and the type of operative procedure Part of the variation is also due to differences in the methods used to measure energy expenditure. In the hospital setting energy expenditure is usually calculated from resting energy expenditure (REE), which includes the basal metabolic rate, energy required for the digestion of food (specific dynamic action of food) and minimal physical activity[33] REE is derived from indirect calorimetric measurements over a 30–40 min period, multiplication of this figure to give a value over 24 h, and adjustment of the resulting figure by an activity factor to provide an estimate of TEE[1]. A fundamental criticism of this technique is that the true relationship of REE to TEE is unknown, although REE is generally thought to account for 75–90 per cent of TEE[33]. Furthermore, the inability of many patients to tolerate nose clips or face masks necessary for indirect calorimetry, particularly in the postoperative period, can result in alterations in the respiratory pattern and consequently in the calculations of energy expenditure[34]

The doubly labelled water technique circumvents many of these problems It is a non-invasive, stable isotope method for measuring TEE over specific time periods, with the advantages of being theoretically simple, safe and of minimal inconvenience to the patient. The doubly labelled water method was described in 1955[11], used for the study of energy expenditure in small animals from then onwards[12], and applied to humans in 1982 by Schoeller and van Santen[13] The technique has an accuracy to within 2–5 per cent of carbon dioxide production rates calculated by whole-body indirect calorimetry[14–17] To date most studies in humans have examined healthy volunteers, babies, pregnant women and patients receiving total parenteral nutrition.

The current report is one of the largest clinically based studies using doubly labelled water and the only one to address the effects of cardiopulmonary bypass and intraoperative hypothermia on energy expenditure There was concern in the preoperative component of our study that, although all patients came from the West of Scotland, different sources of fluid intake might vary in background isotope enrichment and therefore produce changes in the isotopic abundance of body water after administration of doubly labelled water. This concern was reduced by measuring the baseline enrichments of the patient's urine before administration, and also by providing a sufficient dose of doubly labelled water so that background fluctuations would have relatively little influence on the final enrichment of the body water pools. In the postoperative period all study patients received fluid from the same source and the natural abundance of isotopes in the urine of other patients receiving fluid from the same source, but not doubly labelled water, showed only minor variations. There was no significant difference in the body water pool of the study population over the experimental period. In any case, it has been demonstrated that even a 50 per cent change in total body water would affect calculations of energy expenditure by a maximum of 10 per cent[35].

Our study demonstrated a postoperative increase in TEE of 4·7 per cent in the 28°C group and by 5·1 per cent in the 20°C group. When calculated according to lean body mass, the postoperative increases were respectively 3·7 per cent and 3·2 per cent. These results are in accordance with those of Kinney and co-workers who reported that elective surgery of moderate severity produced only modest, i.e. <10 per cent, changes in energy expenditure[1,2]. Our results are in contrast to those of the only other study using doubly labelled water in a surgical setting, which reported increases in postoperative energy expenditure of up to 25 per cent[7]. Interpretation of results in that study was complicated by the fact that all seven patients were women with active Crohn's disease and required total parenteral nutrition[7].

It is possible that the modest postoperative increase in TEE in the current study was due predominantly to an increase in basal metabolic rate, as general activity levels were reduced in the postoperative period. Attempts to measure REE in the postoperative period were abandoned, however, as the patients could not lie comfortably at rest because of discomfort from their sternotomy wound.

In this study[9] a more profound level of intraoperative hypothermia did not attenuate changes in postoperative TEE despite our previous observation of smaller postoperative increases in counter-regulatory hormones in patients undergoing surgery at 20°C. Although counter-regulatory hormones are implicated in the control of changes in postoperative energy expenditure[28–30], our results suggest that they do not exclusively dictate such changes in cardiac surgery patients. It would have been of considerable interest to examine TEE in a group of patients undergoing normothermic cardiopulmonary bypass to elucidate the effects of even moderate hypothermia on postoperative TEE, but in view of current knowledge regarding myocardial preservation this could be considered prejudicial to myocardial safety.

From a practical point of view our results support the view that energy requirements in the uncomplicated postoperative patient can be adequately met with a caloric intake 1·24 times the basal metabolic rate[36], rather than 1·76 times the rate as recommended by some[4].

Despite the obvious attractions of the doubly labelled water technique, clinical application has been delayed because of the expense of the ^{18}O isotope. Although deuterium-labelled water is cheap, sufficient ^{18}O isotope for the current study costs approximately $600 per patient (for both phases of the study). With increasing popularity of the technique and expanding facilities for isotope production, costs are likely to fall. We found the doubly labelled water technique to be an eminently suitable and easily applicable technique for measuring TEE in hospital patients. To detect smaller changes in energy expenditure with confidence, however, would require more precise measurement of fractional turnover rates of deuterium and oxygen. This could be achieved either with larger doses of doubly labelled water or with more frequent analyses, but both options would add considerably to the expense of the study

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Massive incisional hernia: abdominal wall replacement with Marlex® mesh

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Marlex® (polypropylene) mesh was used to replace the abdominal wall in massive incisional herniation in 50 patients. Seventeen unsuccessful attempts at primary repair had previously been made on nine patients. Patient follow-up ranged from 6 to 120 months (mean = 45 months). There was minor hernia recurrence in four (8 per cent) patients. In each instance it was due to partial detachment of the peripheral fixation of the patch. Complications were: wound infection, four (8 per cent); wound seroma, two (4 per cent); wound haematoma, one (2 per cent); and wound sinus, six (12 per cent). Complications did not necessitate removal of the patch in any case. Inadequate peripheral attachment of the patch has been the only cause of hernia recurrence and should be avoidable.

Satisfactory closure of abdominal incisions remains a challenge, with incisional herniation rates of 1–11 per cent still reported[1,2]. Most incisional hernias are small, occur within 3 years of surgery[2], and are satisfactorily repaired using the patient's own tissues and conventional surgical technique[3,4]. This paper concerns massive hernias with large musculofascial defects in the abdominal wall, sometimes extending from the xiphisternum to the pubis. Such hernias are very debilitating, prone to complications, and poorly controlled by external supports. Patients and surgeons alike are discouraged by repeated and often unsuccessful attempts at repair, with many patients confined to a restricted lifestyle. It is our policy to reconstruct the abdominal wall with Marlex® mesh (C. R. Bard Incorporated, Billercia, Massachusetts, USA) in such cases of massive incisional herniation. This is a report of the technique and results in 50 consecutive cases.

Patients and methods

Between January 1981 and June 1989 50 incisional hernias were repaired using Marlex mesh. There were 21 men and 29 women of mean age 57 years (range 33–84 years). Causative incisions were midline (29), paramedian (16), Pfannenstiel (two), and closure of stoma (three). The mean duration of herniation was 78 months (range 6 months to 40 years). The mean area of muscular defect was 173 cm^2 (range 15–450 cm^2). Unsuccessful hernia repair had previously been performed 17 times on a total of nine patients. One patient had five and another patient three attempts at repair before referral. Twenty-six patients had a history of previous wound infection at the site of herniation. No patient referred for incisional hernia repair and considered fit for general anaesthesia was refused surgery. Obese patients were encouraged to lose weight before surgery, and those with evidence of cardiovascular or respiratory disease were admitted 2–3 days before operation for optimization of their medical condition.

Operative technique

A single intravenous dose of flucloxacillin was given before induction of general anaesthesia. An eliptical incision was marked before operation, incorporating any redundant skin, which was excised. The incision was deepened laterally to display the external oblique aponeurosis for a distance of at least 8 cm from the margin of the musculofascial defect around the full circumference. With large defects, this resulted in exposure from the sternum above to the pubis below, and laterally to beyond the midclavicular line. The hernial sac was then opened at its apex and partially excised, leaving sufficient for closure after the hernial contents had been replaced in the abdominal cavity. This was facilitated by omental excision in extremely obese patients. In these cases, the mesh was placed in direct contact with the abdominal contents without subsequent complication.

The technique of insertion of the mesh is illustrated in *Figure 1*. The mesh was cut to a diameter 10 cm greater than that of the musculofascial defect. It was fixed in place with two concentric rings of interrupted 2/0 polypropylene sutures. The inner layer was at or just lateral to the margins of the muscular defect with the outer ring of sutures positioned 1 cm from the periphery of the patch. Sutures were applied at intervals of 1 cm. A big bite of fascia was taken, particularly with the outer ring, but caution was exercised when stitching medially because of the adjacent peritoneum. The first stitches were placed laterally, and the tension of the patch was easily adjusted as the circumferential stitching proceeded. In cases in which the muscular

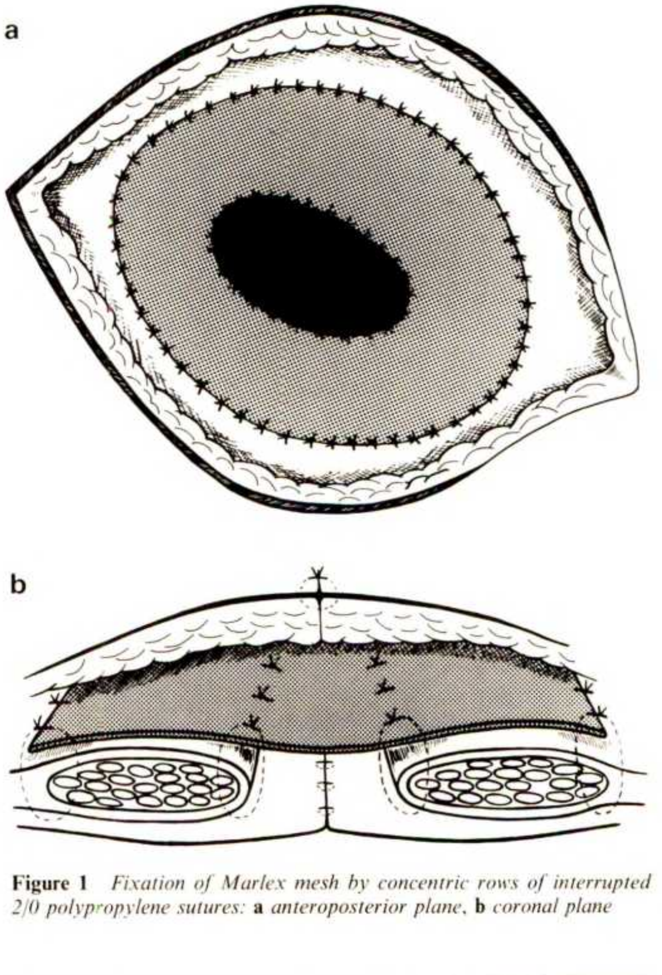

Figure 1 *Fixation of Marlex mesh by concentric rows of interrupted 2/0 polypropylene sutures:* **a** *anteroposterior plane,* **b** *coronal plane*

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defect extended near the xiphisternum or pubis, the patch was sutured directly to the fascia overlying the ribs and thoracic muscles above or the pubic bone below. In such cases the entire Marlex patch (26 x 36 cm) was required Two suction drains were placed in all wounds. Straining was avoided during reversal of anaesthesia and extubation, at which time the surgeon supported the abdominal wall manually.

Results

There was no perioperative mortality. Average postoperative hospital stay was 10 days (range 3–35 days). Patient follow-up ranged from 6 to 120 months (mean 45 months) and was complete for every case. Complications encountered are set out in *Table 1* Minor hernia recurrence occurred in four (8 per cent) patients. These presented at 6, 13, 17 and 19 months after repair. Recurrences were small and resulted from partial peripheral detachment of the mesh from its fascial attachment. Two of these recurrences were easily repaired by local exposure and resuture of the edge of the circumference of the patch. The other two patients with asymptomatic recurrence declined operation and were treated conservatively without complication. One very obese patient achieved marked weight reduction after the repair and subsequently presented with bulging of the mesh. In this case there was no peripheral detachment and no failure of the material. It was decided to incise the patch vertically and to refashion it by overlapping the cut edges.

There were four cases of wound infection (8 per cent) with positive cultures for *Staphylococcus aureus* in two, *Staphylococcus albus* in one and a β-haemolytic streptococcus in one. All infections responded to appropriate antibiotic therapy and none required removal of prosthetic material. Wound sinuses occurred in six patients, only one of whom had wound infection at the time of hernia repair. These sinuses appeared at intervals of 6–18 months after surgery. Two healed spontaneously, two healed after removal of the offending polypropylene sutures, and in two patients excision of a small part of the mesh and accompanying sutures resulted in healing, without detriment to the repair. It was not necessary to remove the polypropylene mesh in any case.

One patient developed small bowel obstruction unrelated to the repair 4 years after surgery This was successfully managed at laparotomy, by dividing the patch in the vertical axis, and closed by overlap and suture without subsequent morbidity. A patient with chronic renal failure had repair of a large incisional hernia and insertion of a Tenchoff dialysis catheter at the same operation. Subsequent episodes of both bacterial and fungal peritonitis related to continuing peritoneal dialysis were treated with appropriate antibiotic therapy without removal of either catheter or mesh.

Discussion

Incisional hernias should be repaired unless the patient is unable or unwilling to undergo surgery, as hernias increase in size, are unsightly and frequently painful, and may eventually cause bowel obstruction[5]. The recurrence rate usually varies directly with the size of the defect and, with large hernias closed under tension, may be as high as 20 per cent[5].

Prosthetic materials were introduced to help close large defects and a variety of non-biological materials have been used. Marlex mesh has been the most widely used prosthetic material since its introduction[6]. It is a knitted monofilament mesh which does not disintegrate with age, is pliable and easy to use, has a two-way stretch that allows for more even load distribution, and in experimental studies provided fewer adhesions than other plastic meshes[7]. In clinical practice, however, a variety of complications including infection and sinus formation have been described[8]. Previously reported complications of mesh extrusion[9], erosion into viscera[10] and bowel fistula[11] were not experienced in this study.

The hernia recurrence rate reported here (8 per cent) is comparable with the 6–10 per cent of other series using Marlex mesh in incisional hernias, although duration of follow-up has not been as long as in the present series (mean 45 months)[6,12,13] Usher has also reported a 0 per cent recurrence rate in 48 patients with a 6–36-month follow-up period[14]. Avoidance of the technical errors of inadequate fixation of the periphery of the patch and fixation to weakened fascia should further reduce recurrence rates.

Wound sinus formation in this study was high (12 per cent) compared with the 0–3 per cent reported in comparable studies[6,13]. Sinuses were not attended by any serious complications, however, and were effectively treated by minor surgical procedures.

The wound infection rate of 8 per cent was comparable with other reported series which had rates of up to 10 per cent[4,15] Lewis[13] and Usher[6] have reported infection rates of 4 and 6 per cent respectively using a policy of selective antibiotic prophylaxis before Marlex mesh repair of incisional hernias. Lewis cultured *Staphylococcus aureus* from suture granulomata in two of 14 patients who had a history of previous infection, although none developed infection when given antibiotic prophylaxis[13]. Over half of the patients in the present series had such a history of previous wound infection. Reactivation of such old infection is an important risk factor for subsequent development of wound infection Other risk factors for infection seen in the present group include the high number of recurrent hernias (nine of 50), and the use of suction drains in all patients[15]. This combination of multiple risk factors in patients undergoing repair has led us to use prophylactic antibiotics in all cases.

Although Marlex mesh has been the most widely used prosthetic material to date, expanded polytetrafluoroethylene (Gore-tex® soft tissue patch, W. L. Gore and Associates Incorporated, Flagstaff, Arizona, USA) has been reported to possess several advantages. Reports suggest that, in the experimental situation, it elicits a low foreign body reaction[16], has a low infection rate[17], exhibits a low rate of adhesion formation[18], and supports fibrous tissue incorporation[19]. As a result of these characteristics, a lower incidence of sinus formation and a lesser tendency to erode abdominal viscera would be expected. However, when compared with the present study, expanded polytetrafluoroethylene had a lower incidence of sinus formation but a similar incidence of wound infection. However, reherniation was more common (11 per cent) than the 8 per cent reported here[20].

Raised intra-abdominal pressure after repair was not found to be a problem in this series. Historically, increases in pressure have been caused by ill-advised attempts to approximate the edges of large defects. No such attempt was made in our patients. In all cases, eviscerated bowel was easily accommodated within the abdomen, and the patch was sutured in place under moderate tension. In no patient was it necessary to induce a pneumoperitoneum before surgery, and no patient required ventilation after operation.

In comparing series from the literature, it is difficult to be sure that like is being compared with like. It is obvious that the use of prosthetic mesh will give excellent results in small hernias, and results from series that include massive eviscerations which have had multiple previous attempts at repair are likely to be less satisfactory. In this study, which included nine (18 per cent) tertiary referrals, no patient fit for surgery was refused operation. It is the authors' policy to repair all incisional hernias, irrespective of size, provided the patient is fit for surgery. Most small incisional hernias can be repaired using the patient's own tissues, without tension In cases where

Table 1 *Abdominal wall replacement with Marlex mesh* (n=*50*)

Complication	*n*	%
Hernia recurrence	4	8
Wound infection	4	8
Wound seroma	2	4
Wound haematoma	1	2
Wound sinus	6	12

this is not possible, we have found Marlex mesh a valuable alternative. Its use is associated with an acceptably low incidence of reherniation and complications, and it compares favourably with other prosthetic material.

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245–246

Where there is no anaesthetist ...

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In an unselected series of 254 operations representing a wide range of surgical, obstetric and gynaecological procedures carried out on the small Pacific island of Tuvalu, the majority (85 per cent) involved the lower half of the body. In all cases but one anaesthesia was administered by a non-specialist. In operations below the level of the diaphragm epidural anaesthesia was usually used with a success rate of 96 per cent. In the upper half of the body ketamine was used where local or regional block was insufficient. Only one operation was performed under general inhalation anaesthesia. The overall postoperative mortality rate was 0·4 per cent and the morbidity rate was 13 per cent. Only two minor complications were attributed to the anaesthetic method used. In situations where anaesthetists are not available, epidural and ketamine anaesthesia in the hands of non-specialists are safe and practical options to general inhalation anaesthesia and are appropriate for most surgical procedures.

Lack of a qualified anaesthetist is unusual in Western surgical practice. With international cooperation, however, surgical services are provided in places with limited facilities. Administration of general inhalation anaesthesia with controlled ventilation requires knowledge and experience. Safe options, accessible to a surgeon or general practitioner and covering most of the needs of basic surgery, are available and can be used with good results as this material from the Pacific islands of Tuvalu illustrates.

Tuvalu comprises nine atoll islands in the central Pacific with a population of about 9000 people. The only hospital, the Princess Margaret Hospital in the capital Funafuti, has 35 beds, basic laboratory and radiological services and a surgical theatre with one operating table. Of the three Tuvaluan general practitioners, one has limited experience in the administration of epidural, spinal and ketamine anaesthesia. The author worked in Tuvalu as a United Nations volunteer surgeon for 21 months during 1988 to 1989.

Patients and methods

A total of 316 operations were performed during the 21 months. A visiting team of Australian ophthalmologists carried out 39 procedures under optic nerve and regional block. Visiting Australian plastic surgeons operated on three patients (two local, one arm block) and Tuvaluan doctors performed two operations (both under epidural), which are not included in this study. The author operated on 18 day-case patients (17 local, one ketamine), these were also excluded. The remaining 254 operations representing a wide range of surgical procedures and performed by one surgeon form the basis of this study.

Preoperative evaluation consisted of clinical examination and haemoglobin determination. Urine glucose and protein were excluded. Where significant blood loss was anticipated, blood grouping was carried out and potential donors cross-matched. Preoperative medication included promethazine 12·5–25 mg (for adults) intramuscularly and pethidine 1 mg/kg intramuscularly for all except patients undergoing caesarian section. When ketamine was used, atropine 0·01 mg/kg intramuscularly and diazepam 5–10 mg intravenously (for adults) were given shortly before induction.

A single-shot lumbar epidural anaesthesia with 18–20 ml of 0·5 per cent bupivacaine with adrenaline was administered through an epidural needle using glass syringes and loss of resistance technique. Spinal anaesthesia was achieved with injection of 2·5–3·0 ml of hyperbaric cinchocaine mixed with 0·1 ml adrenaline (1:1000) with a thin spinal needle through the L2–L3 interspace into the subarachnoid space. The patient was placed supine immediately, the head was tilted down and the level of analgesia was checked with the 'pin-prick' method until the desired level was reached. Prehydration with 1000 ml of lactated Ringer solution was used for adult patients with epidural or spinal anaesthesia.

Ketamine anaesthesia was induced with 1–2 mg/kg of ketamine given intravenously as a bolus and half the original dose was repeated as needed. With small children the intramuscular route was used. At the end of the operation adult patients received an additional dose of diazepam (5 mg intravenously).

Submaximal doses of lignocaine with or without adrenaline were used for local infiltration, digital and arm blocks.

Intraoperative monitoring was by clinical assessment because no cardiac monitors were available.

Postoperative care in the wards was performed by the patient's relatives (caretakers) and supervised by the ward nurses.

Results

A total of 244 patients underwent 254 operations. Their mean age was 33 years (range 1 month–83 years) and 173 (71 per cent) were female. Of the 244 primary operations 99 (41 per cent) were emergency operations. Prophylactic antibiotics were used in 134 of 244 cases (55 per cent).

The anatomical regions and more common procedures are summarized in *Table 1*. Operations below the level of the diaphragm comprised 85 per cent of the total. All 17 laparotomies were carried out through vertical midline or paramedian incisions and consisted of eight ovarian cystectomies, three operations for generalized peritonitis, two small bowel resections, two hysterectomies and two explorative laparotomies. Of the 61 operations in the anogenital region, dilatation and curettage was carried out on 38 occasions and hydrocoelectomy on 11.

The majority of operations in lower extremities were carried out for complications of septic wounds, skin necrosis and

Table 1 *Anatomical regions and more common procedures of the 254 operations*

Region	No of operations
Anterior abdomen	131
Caesarean section (40)	
Tubal ligation (32)	
Appendicectomy (24)	
Laparotomy (17)	
External hernia repair (9)	
Miscellaneous (9)	
Anogenital region	61
Lower extremity	21
Female breast/chest wall	17
Head/neck	12
Upper extremity	10
Lower back	2

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Table 2 *Principal anaesthetic methods used in 254 operations*

Method	No. of cases
Epidural	156
Ketamine	55
Local infiltration*	29
Spinal	8
Sedation only	2
General inhalation anaesthesia	1
Arm block	1
None	2

* Includes digital blocks

gangrene and included debridement (six cases), split-skin grafting or secondary closure (five cases) and below-knee amputation (three cases). Two sequestrectomies (one femur, one fibula) for chronic osteomyelitis were also done. Of the 17 female breast or chest wall operations, one was a mastectomy and the remaining were partial resections or tumour excisions.

Most of the operations involving the neck were excisions of simple lesions (two lipomas, two tuberculous glands, one branchial cyst, one metastatic gland) but one partial parotidectomy and a drainage of a deep neck abscess were also carried out. Elevation of a depressed skull fracture, exploratory burr holes, sequestrectomy for chronic osteomyelitis of the skull and excision and skin grafting of a nose tumour completed the total. Secondary repair of median and ulnar nerves at the wrist (in one patient) and removal of a large sequestrum in the humerus were among the operations for upper extremity and were both carried out under ketamine anaesthesia.

The methods of anaesthesia for the 254 operations are listed in *Table 2*. Epidural anaesthesia failed or was incomplete in seven cases and was completed with ketamine in five cases, local infiltration in one and general inhalation anaesthesia given by a visiting anaesthetist from an ophthalmic team in one case. One insufficient local infiltration anaesthesia and one failed arm block were completed with ketamine.

There was one postoperative death from cerebral contusion after a motor vehicle accident. Exploratory burr holes were performed without anaesthesia to the deeply unconscious patient but no treatable lesions were found and the patient died 5 h after the operation. In addition, two babies died after caesarean section. One had multiple anomalies of the head and extremities and died within an hour of delivery. The other was a retained second twin who died 2 days after operation from sepsis.

Thirty-two patients (13 per cent) had a total of 35 postoperative complications. The majority were wound complications (25 cases), others included joint pain (two cases), partial facial nerve paralysis (two cases), haemorrhage (one case), urine infection (one case), paralytic ileus (one case) and fever of unknown origin (one case). Two postoperative complications could be attributed to the anaesthetic method. One patient undergoing laparotomy for a large (6·2 kg) ovarian cyst under spinal anaesthesia developed postoperative hypotension which was successfully corrected with infusion of metaraminol. Another patient had weakness of one leg after epidural anaesthesia which subsided spontaneously within 3 days.

The mean hospital stay for survivors was 13 days (range 1–138 days).

Discussion

In this series, there were 125 obstetric and gynaecological operations in a total of 254 operations (49 per cent). Most abdominal operations were performed through lower abdominal or inguinal incisions. Epidural anaesthesia was the method of choice for most operations below the diaphragm. When better muscle relaxation was needed spinal anaesthesia was used. Ketamine was administered when the procedure was urgent or of short duration. It was also useful when epidural anaesthesia failed or was incomplete which occurred in seven of 163 (4 per cent) cases.

Compared with general anaesthesia, regional anaesthesia has less early mortality and appears to reduce morbidity in operations below the umbilicus[1]. Epidural anaesthesia enhances gastric emptying[2] and increases stomach and small bowel electrical activity[3] which could contribute to a lower incidence of postoperative paralytic ileus. Decrease in intraoperative blood loss, postoperative catabolism, thromboembolic and pulmonary complications have been reported[4]. Epidural analgesia for caesarean section is associated with less fetal depression and higher Apgar scores than general anaesthesia[5].

No thoracotomies were performed but epidural anaesthesia may be successfully used for thoracic surgical procedures on awake, spontaneously breathing patients[6].

Ketamine is widely used as an anaesthetic in the treatment of battle casualties[7] and in this series was mainly used for surgery of the upper half of the body when local infiltration or regional block were not applicable. Draining of abscesses, excision of neck tumours and operations on the female breast are suitable procedures for ketamine anaesthesia.

Ketamine should not be used for patients with head injuries, and one elevation of a depressed skull fracture was successfully performed using local infiltration anaesthesia.

Postoperative restlessness and hallucinations associated with ketamine were effectively controlled with diazepam. The quiet environment and presence of a close relative as a caretaker must have had an additional beneficial effect.

Unexpected anaesthetic mortality occurs infrequently, 1:3000 or 0·04 per cent[8], which makes the number of cases in this report too small for conclusions to be drawn. The two complications in the series (0·8 per cent) attributable to the anaesthetic method used can be classified as minor, according to Derrington and Smith being less than the reported 0·4 per cent for major and 8·9–9·4 per cent for minor anaesthetic complications[9].

A qualified anaesthetist is essential for the safe conduct of inhalation anaesthesia but when not available a wide range of operations can be carried out safely using epidural or ketamine anaesthesia administered by a non-specialist.

Acknowledgements

I wish to thank my colleagues and the staff at the Princess Margaret Hospital in Tuvalu for their help and dedication and especially Dr Teleke Kofe who administered most of the anaesthesias presented in this article

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Management of disc battery ingestion in children

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Small flat disc batteries are used as energy sources for a wide variety of products such as watches, hearing aids, cameras, calculators and recently children's toys. They are present in most homes, within the reach of children and accidental ingestion of such batteries is potentially dangerous.

There are four principal types of disc battery and their toxic constituents are as follows: (1) mercury cell containing mercuric oxide and aqueous potassium hydroxide; (2) alkaline manganese cell containing manganese dioxide and aqueous potassium hydroxide; (3) silver cell containing silver oxide and aqueous potassium hydroxide; and (4) lithium manganese dioxide cell containing lithium and manganese dioxide.

Lithium cells are mostly used in watches where replacement is normally by a specialist, thereby limiting access to children. They are more resistant to corrosion than other disc batteries and have not caused problems when swallowed as their thin shape facilitates gut transit. They seem to be non-toxic when swallowed[1,2]. The most common types of batteries used are the mercury cells and they are by far the most dangerous.

Ingested disc batteries pose problems when they become lodged in the gut and when they become corroded and release their toxic contents. All disc batteries contain significant amounts of potassium hydroxide and if a battery becomes lodged, especially in the oesophagus, it may cause complications of caustic injury including oesophageal perforation and tracheo-oesophageal fistula[3,4]. Mercury cell batteries contain potentially lethal quantities of mercury and if these break open in the stomach or lower bowel, they release soluble mercury salts which may give manifestations of acute mercury poisoning (abdominal pain, diarrhoea and vomiting, inflammation of mucous membranes with excessive salivation, and central nervous system effects resembling parkinsonism with personality changes and tremors). The kidney is the major target organ and renal tubular necrosis and nephrotic syndrome may develop[5].

When undischarged cells are swallowed, the electric current produced by the battery causes a rise of the pH at the anode surface. It is this, possibly combined with local short circuit current through the tissues, that might cause tissue burns, especially if the battery is lodged in the oesophagus and in the very rare event of it lodging in Meckel's diverticulum, resulting in perforation[6,7]

Case reports

At Yeovil District Hospital, five children were admitted with disc battery ingestion over the past year. Their ages ranged from 18 to 24 months. They were all asymptomatic. Chest and abdominal radiographs on admission revealed the disc batteries in the stomach Gastroscopy was successful in removing the disc battery from the stomach in only one case. The other four infants passed the battery spontaneously during the following 24 h without event or complication

A management protocol was instituted as follows (1) Determine the type of battery. Spare batteries are often kept at home and will provide a useful guide. Ascertain whether the battery was new or exhausted, as worn-out batteries are generally less toxic. (2) Perform plain chest and abdominal radiographs to determine the position of the battery (3) If the battery is in the oesophagus immediate endoscopic removal is indicated. (4) If the battery is in the stomach and intact, the patient is admitted to hospital for observation, given oral cimetidine or ranitidine to reduce gastric acid and the passage of the battery is followed by daily abdominal radiographs. (5) If the battery remains in the stomach for more than 24 h endoscopic or surgical removal is mandatory. (6) If there is radiological evidence of leakage (disc battery contents are radio-opaque), the battery breaking open, signs of peritoneal irritation or manifestation of mercury poisoning then endoscopic or surgical removal is performed and blood mercury levels are measured (normal blood mercury level is below 6 μg/l). If elevated the patient should be treated by a mercury-chelating agent such as dimercaprol[8].

Discussion

Successful spontaneous passage occurs following disc battery ingestion in the majority of cases and only 10 per cent of patients develop symptoms[2]. Fortunately the children who swallowed disc batteries who were managed at Yeovil District Hospital did not develop complications. The purpose of this paper is to emphasize the potential danger of disc batteries and to propose a management protocol.

Acknowledgements

I would like to express my gratitude to Mr P. Knipe and Mr D. A Griffiths, consultant surgeons at Yeovil District Hospital for advice and guidance during the preparation of this paper and their permission to include their patients in the study

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Infection and the burn patient

Sir

The leading article by Pruitt (*Br J Surg* 1990; **77**: 1081–2) concentrates essentially on skin flora acting as the main source of infection in burn patients. Several recently described papers suggest that the intestinal tract may also be an important source of sepsis in the critically ill burn patient.

First, changes in intestinal permeability have been proposed as essential in the pathogenesis of several gastrointestinal tract disorders, notably inflammatory bowel disease[1–5]. Studies in both animal models[6] and in man[7] indicate that intestinal permability is increased in the burn patient.

Second, work from Bulkley's group[8,9] has shown the importance of gut ischaemia and hyperpermeability as a source of sepsis in the critically ill surgical patient leading to multiple organ failure, probably by altering splanchnic haemodynamics.

Third, work from Wilmore's laboratory[10] would imply that increased gut permeability is associated with changes in levels of tumour necrosis factor, endotoxin, fibronectins and complement derived products.

From these separate mechanisms it is clear that in burns, elevated gut permeability may allow bacterial toxins to enter the portal blood stream. Because of the increased susceptibility of the host associated with hypocomplementaemia and consumption of fibronectins, the toxins may be particularly virulent in the systemic circulation[11].

The possible central role of gut flora in burn sepsis should therefore stimulate a re-evaluation of the use of selective intestinal antibiotic decontamination in the seriously ill patient with burns, as well as careful monitoring of intestinal permeability and the use of therapeutic measures directed towards correcting any defects.

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Letter 2

Sir

Dr Pruitt in his leading article (*Br J Surg* 1990; **77**: 1081–2) quotes the well known question, 'Can .. the leopard change his spots?' The quotation was, of course, used by Mr Rudyard Kipling but has a much more ancient origin, the priority going to a Hebrew prophet (Jeremiah 13; 23) some centuries before Christ Taken in context the answer to the question would appear to be a very definite 'no' Apparently human nature is more immutable than the specificity of organisms causing wound infection. Even the famous Balm of Gilead proved inadequate to the task (Jeremiah 8: 22) Such a radical transformation is beyond the art of the physician and calls forth the prescription of the prophet

Dr Pruitt has, I am sure, been successful in evoking the interest of subscribers to the Journal. I have a high regard for his authority in the area of burn treatment but perhaps the suggestion that the prophet's tears represented some kind of topical agent is slightly eccentric. Jeremiah is, I think, unfairly represented in many quarters as a pessimist. Rather he was realistic in his diagnosis of moral evil which had no human cure, balanced by an unquenchable hope of a divine cure his tears were, therefore, not so much a topical agent as a plea for divine intervention from outside the situation.

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Letter 3

Sir

Shame on you for allowing Dr Pruitt to attribute this quote to Kipling.

The correct author was the prophet Jeremiah (c. 628–586 BC) and the couplet in full is·

> *Can the Ethiopian change his skin or the leopard his spots?*
> *Neither can you do good who are accustomed to doing evil.*
> Jeremiah 13·23
> New International Version

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Author's reply

Sir

The quotation by Rudyard Kipling that I used as the title for the leading article that I prepared was selected to evoke the interest, not the jeremiads, of the subscribers In the copy of *Just So Stories* that I have, no reference is provided for the quotation and I was unaware of Jeremiah's priority. I assume that Kipling's readers had greater biblical literacy than I have and he felt it unnecessary to make attribution of the quotation.

Mr Millar's conclusion that human nature is more immutable than organisms causing wound infections is, I feel, too pessimistic. Even Jeremiah in the last verse of Chapter 13 implies that Jerusalem can actually lose its spots when he asked, 'How long will it yet be before you come clean?' In Chapter 8, to which Mr Millar makes reference, Jeremiah decries the ineffectiveness of the Balm of Gilead in healing the moral wound of the people of Zion but, in the opening verse of Chapter 9, he suggests that the tears of the prophet would be therapeutic Such therapy is certainly the lineal ancestor of water soluble topical agents that provide the optimum protection against invasive burn wound infection.

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Intraoperative air testing of colorectal anastomoses

Sir

Of two reports concerning intraoperative testing of colorectal anastomoses, Beard *et al.* (*Br J Surg* 1990; 77: 1095–7) described the effectiveness of air testing using a sigmoidoscope, while Pitchard *et al* (*Br J Surg* 1990, 77: 1105) did air testing using a bladder syringe which might be misleading for low colorectal anastomoses using the double stapler techniques. An intraoperative leak test is performed to determine whether or not the anastomosis is air tight. However, airtight anastomoses do not guarantee complete prevention of the postoperative leak.

Recently, we have employed the urological cather with quadrant large holes (Malecot Model Drain, C. R. Bard Incorporated, Covington, Georgia, USA) for intraoperative air testing after colorectal anastomoses. A Foley catheter balloon may disrupt low anastomoses, but the procedure has the advantage of simplicity compared to the use of a sigmoidoscope. The advantage of sigmoidoscopy is the ability to observe the anastomoses directly. A Malecot catheter equipped with large holes has been useful and easy for not only air testing but also draining the residual faeces and for rectal washout. Furthermore, we positioned the catheter above the anal sphincter and connected it to a closed drainage system to decrease the intrarectal pressure in the first 5 days after operation. Anorectal manometry showed an increase of intrarectal pressure when flatus was passed[1]. Then, catheter drainage of flatus and faeces decompressed the anastomosed neorectum. Also we can perform a limited water-soluble contrast enema through the Malecot catheter before withdrawing it.

Seventy-eight consecutive patients who underwent colorectal anastomoses with air testing by using the Malecot catheter have been evaluated. Six patients were found to have an air leak, added reinforcing sutures or a covering stoma. Two of them developed postoperative leakage. Three patients whose anastomoses were air tight developed postoperative leakage. We reduced the postoperative leak rate from 18 to 7 per cent by an introduction of a Malecot catheter.

As Dr Pitchard described, leakage must be the result of factors other than the construction of structurally sound staple lines. We choose a Malecot catheter not only to make a sound anastomosis but also to minimize postoperative anastomotic hazard caused from intraluminal problems. It is an important concept that the surgeon should give special attention to the anastomosis.

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1 Miller R, Lewis GT, Bartolo DCC, Cerbero F, Mortensen NJMcC: Sensory discrimination and dynamic activity in the anorectum: evidence using a new ambulatory technique. *Br J Surg 1988*, 75: 1003–7

Letter 2

Sir

I was interested to read two accounts of intraoperative air testing of colorectal anastomoses in the Journal (*Br J Surg* 1990, 77: 1095–7 and 1105).

Many years ago I was performing more longitudinal myotomies for certain cases of diverticular disease and I used a similar method to detect any accidental leak, but I employed an old fashioned Higginson syringe which was attached by extension tubing to a Foley catheter inserted into the lower rectum. The syringe bulb was placed on the floor and was able to be compressed by the surgeon himself who was of course watching the field inside the pelvis. In this way there was no inco-ordination which might exist between two operators, and it allowed very careful control of the amount of air being injected.

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Letter 3

Sir

In the October issue two papers were published on intraoperative testing of colorectal anastomoses (*Br J Surg* 1990, 77: 1095–7, 1105). Both papers concluded that this was a useful procedure but both also concluded that it had limitations.

In the first study a radiological leak was detected after operation in 11 per cent of anastomoses and 4 per cent developed a clinical leak despite no leak being detected at intraoperative testing. In the second study, 10 per cent of anastomoses developed a clinical leak despite intraoperative testing. This suggests that the idea of intraoperative testing is valid but that its execution could be improved.

Both papers kindly referred to previous work on this method[1] and yet chose to differ in one critical essential. In neither paper did the method of testing include any indication of the pressure to which the anastomoses were being subjected. In previous work it was shown that a pressure of at least 25 cmH_2O was required to detect anastomotic defects[1]. This was achieved by distending with saline via tubing attached to a manometer as used for central venous pressure monitoring. No deleterious effects were encountered in the original study nor, to date, in further work which is still in progress.

Intraoperative anastomotic testing should continue to be used, but unless the anastomoses are subjected to sufficient pressure some imperfections in technique will still pass unnoticed and lead to postoperative leaks. It is suggested that this occurred in both these studies. At present the recommendation is for 25 cmH_2O pressure but further research may amend this figure.

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1 Gilbert JM, Trapnell JE. Intraoperative testing of the integrity of left-sided colorectal anastomoses: a technique of value to the surgeon in training. *Ann R Coll Surg Engl* 1988; 70: 158–60

Authors' reply 1

Sir

Mr Gilbert is probably correct in suggesting that the results of intraoperative testing of colorectal anastomoses might be improved by measurement of the pressure. However, our aim was to use a method of testing which was simple, quick and acceptable to most surgeons. The addition of pressure monitoring is a council of perfection, which most surgeons would probably ignore.

Most of the clinical leaks that were not detected by intraoperative testing occurred in the double stapled group. It is likely that some of these leaks were due to ischaemia at the intersection of the staple lines. One could not expect any form of testing to detect these potential leaks.

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Authors' reply 2

Sir

Thankyou for the opportunity to reply to the letter from Mr Gilbert. Our study showed that *per anum* insufflation of air via a syringe was not a reliable method for predicting postoperative leakage from low rectal anastomoses, and we accept the criticism that failure to insufflate to a measured minimum pressure might have led to spurious results. As in much of operative surgery we relied on the tactile sensation of the surgeon to assess the degree of distension in the anastomosed bowel. The validity of this approach is simple to evaluate and we have now set up such a study. However, we believe that the cause of postoperative leakage is multifactorial and anastomoses which appear mechanically sound on intraoperative testing, by whatever method, may subsequently leak.

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Gallstone ileus

Sir

We disagree with the conclusions drawn in the paper by Clavien *et al.* (*Br J Surg* 1990; **77**: 737–42). The paper quite rightly points out that we are dealing with an elderly group of patients many of whom have serious concomitant disease. These patients are often markedly dehydrated and septic at the time of operation due to the unfortunate but common occurrence of delayed presentation and diagnosis. Yet the conclusions are that we should (when feasible and when cholelithiasis has been shown) carry out an extended and sometimes difficult operative procedure Clavien *et al* base their claims on the following points.

First, that there appeared to be no significant difference in mortality between the three groups of patients. If, however, we look at the patients who had surgery focussed on the obstructing stones alone it appears that this is not an homogeneous group. Two had small bowel resections and one a Hartmann's procedure. These patients surely form a separate group (complicated gallstone ileus) as opposed to enterolithotomy alone to which we feel the one stage procedure should be compared. The authors unfortunately do not make it clear which operative procedures preceded individual deaths though it would appear that two of the seven deaths occurred after relaparotomy for leakage from intestinal suture lines. If these represent the patients who had bowel resections then this could possibly influence the results depicted and show the relatively simple procedure of enterolithotomy alone to have a lower mortality.

Second, they argue that removing the gallbladder prevents further symptoms such as; (1) repeated gallstone ileus, (2) cholangitis and (3) carcinoma of the gallbladder, and while this is an undeniable fact, it raises the question: 'Is the risk of developing these complications greater than the risk of removing the gallbladder at the initial operation?' This question remains unanswered by the paper.

Recurrent gallstone ileus in most reports has a lower incidence than in this review. The two early recurrences may even be explained by failure to detect a second stone already within the bowel at the original operation. Even if this were not the case it is likely that 80 per cent of stones passing through a fistula will pass the bowel without problem[1].

Acute cholangitis following gallstone ileus should only occur in circumstances when the fistula or cystic duct is no longer patent (even if the organisms originate in the fistula), and there is obstruction within the common bile duct. The frequency of cholangitis with concomitant common bile duct stones reported by Safaie-Shiazi *et al.*[2] in 47 patients with biliary enteric fistula without intestinal obstruction would tend to support this view. Under these circumstances, endoscopic sphincterotomy would be the first treatment of choice in such patients, operation being reserved for those in whom this was unsuccessful.

In the paper by Bossart *et al.*[3] we can find no comparison between the incidence of gallbladder cancer in patients undergoing cholecystectomy and those with biliary enteric fistulae. Even if there were a higher incidence of carcinoma of the gallbladder the carcinoma could have an aetiological role in the formation of the fistula.

It should be noted that none of the patients followed up in Clavien *et al.*'s study died of causes related to further biliary disease We have based our view of this condition on our own review of 43 patients (unpublished data)

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1. Piedad OH, Wels PB. Spontaneous internal biliary fistula, obstructive and non-obstructive types. *Ann Surg* 1972; **175**· 75–80.
2. Safaie-Shirazi S, Zike W, Printen KJ Spontaneous enterobiliary fistulas *Surg Gynecol Obstet* 1973; **137**. 769–72
3. Bossart PA, Patterson AH, Zintie HA Carcinoma of the gallbladder *Am J Surg* 1962; **103**: 361.4.

Author's reply

Sir

We are grateful for the interest shown in our paper on gallstone ileus. The disease is so infrequent that most series are spread over more than 25 years and contain fewer than 30 patients. Our own series of 37 patients was collected over 12 years. The relative rarity of the disease makes randomized trials of treatment difficult, perhaps impossible and so the detailed examination of retrospective data with very careful follow-up of patients is required.

The concern on an apparent inhomogeneity within groups expressed in the latter regarding our paper is understandable, but examination of the detailed data in the paper will show that bowel resection was performed in patients that had cholecystectomy as well as those that did not. This feature was not responsible for the difference in outcome. Our results point to a clear advantage to using a selective one stage procedure (i e. removal of the impacted stone, fistula repair and cholecystectomy), when there is residual cholelithiasis and when local and general conditions are satisfactory. These represent a change from prevailing opinion in this area, and we believe that this change may be due to the increased safety of surgery in the elderly in the past decade. The authors of the letter base their opinion on their own unpublished series. We look forward to the convincing demonstration of their view that selective cholecystectomy is unwarranted from their data.

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Parathyroid autotransplantation

Sir

In their review article Senapati and Young (*Br J Surg* 1990; **77**: 1171–4) state that 'there is a good case for total parathyroidectomy with autotransplantation in the management of renal osteodystrophy', although they concede that 'the benefits are neither predictable nor guaranteed'

Autotransplantation has previously been the policy of our unit following parathyroidectomy for tertiary hyperparathyroidism[1]. However, we have now abandoned the procedure because of the erratic initial response and the increasing late incidence of hypercalcaemia.

Between 1984 and 1990 we have performed 34 total parathyroidectomies including 18 autotransplants Median follow up of the implant group is 40 months (range 12–74 months) and for those without implants 27 months (range 5–68 months).

At one year 76 per cent of implant patients were on vitamin D and/or calcium supplements, indicating that the implanted parathyroid tissue was not functioning. Thereafter, there was a steadily increasing incidence of hypercalcaemia with 50 per cent of implant patients hypercalcaemic by 3 years. The current status of the patients with parathyroid implants is as follows:

	n
Hypercalcaemia	7
Normocalcaemic, no vitamin D	4*
Normocalcaemia plus vitamin D	6
Total	18†

* One patient died 1 year after operation, now only 3 patients in this group. † One patient died one month after operation

The median interval to the development of hypercalcaemia was 45 months (range 8–66 months). In all hypercalcaemic patients there was evidence of recurrent hyperparathyroidism with raised blood PTH levels None of the non-implant patients have so far become hypercalcaemic although three are now normocalcaemic of vitamin D

The development of late hypercalcaemia following total parathyroidectomy without implantation has been previously reported[2]. Farrington *et al* found that 6 out of 7 patients had normal or raised PTH levels when tested 6–9 years post-parathyroidectomy In all seven cases there had been no detectable PTH on radioimmunoassay at 1–2 years after operation The stimulus of uraemia may provoke hyperplasia in an originally quiescent fifth gland or generate activity in embryonic rests of parathyroid tissue in the neck or gland fragments left after the original surgery One patient in our own series became hypercalcaemic 4 years after a successful four gland parathyroidectomy and had a large hyperplastic parathyroid removed from the superior mediastinum.

The presence of an implant complicates the management of the patient who develops hypercalcaemia on follow-up – is the problem due to an overactive implant or recurrent active parathyroid tissue in the neck? The results of venous sampling from the arm can be equivocal and, in our own experience, excision of the muscle segment containing the implant has not universally been followed by restoration of normocalcaemia. Although parathyroid carcinoma is rare we have had one case in a renal patient with tertiary hyperparathyroidism. Carcinoma is difficult to detect on frozen section and it would be extremely unfortunate if an autotransplant of malignant cells was performed.

Medical control of hypocalcaemia is relatively straight forward, especially after kidney translantation. In view of the established late incidence of hypercalcaemia after total parathyroidectomy we feel that the practice of autotransplantation should be abandoned.

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1. Welsh CL, Taylor GW, Cattell WR, Baker LRI Parathyroid surgery in chronic renal failure. subtotal parathyroidectomy or autotransplantation? *Br J Surg* 1984; **71** 591–2
2. Farrington K, Varghese Z, Chan MK *et al* How complete is parathyroidectomy in uraemia? *Br Med J* 1987, **294**. 743.

'Mind the gap'

Sir

Almost any traveller on the London Underground may periodically hear the stentorian tones that seems to surround them from the heavens above before the doors open to more earthly stations 'mind the gap!'

This phrase has set thinking at least one recent long-term visitor to London. It may be yet another example of the common language that divides us, but it may be infused with new meaning for one who shuttles requently between developing and developed worlds.

I am the product of the best of American medical education systems, and have recently taken sabbatical advantage of the University of London School of Hygiene and Tropical Medicine to learn more about advances in our understanding of Third-World health and healthcare delivery problems I am equipped with polymerase chain reaction technology to amplify minute quantities of antigens so that a molecular biologic routine cookbook sequence can be used to raise monoclonal antibodies to these targeted proteins. Immunoradioassay has made possible precise diagnosis of exposure to even subvirion particles, helpful in explaining the epidemiology and potential management methods for hepatitis and AIDS. And, I have just returned from the American College of Surgeons Clinical Congress in San Francisco in which 'Nintendo surgery' is all the rage – probing, zapping and vaporizing any miscreant tissue with an endoscopic guided laser

Then, I return to Africa.

In my Developed World, immunization has made possible such rarity in previously common diseases, that a busy practitioner can spend a lifetime without encountering a case of, for example, tetanus. After all, there were only 100 cases in the Developed World last year; or, 100 cases per hour from the perspective of the undercounted numbers of such a common cause of death in this continent.

Laparoscopic herniorrhaphy is advocated by multiple exhibits at the Clinical Congress just attended – for whatever reason I am unsure, against the competing advantages of outpatient hernia repair with local anaesthesia which has become standardized. That we can debate the application of high or intermediate technology by over-qualified personnel in the solution of such a ubiquitous and simple problem is symptomatic of surgical hypermaturity in this past decade of the 20th century But, mind the gap!

It was pointed our within the pages of this Journal[1] that a victim of strangulated hernia in the dark continent had a one in eight chance of ever encountering any surgical care, let alone a real surgeon performing it. And illness less hyperacute and remarkable has an even lesser chance encounter with medical care or still less effective relief. The gap widens. Do you mind?

By what standard can this decade be called the 'Golden Age of Surgery' when we simultaneously debate the success rate of endoscopic herniorrhaphy using various laser energies and tolerate, if we even know, a failure rate for lack of even trying of over 85 per cent for more obvious stages of the same problem in the world's other half?

Mind the gap!

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1. Nordberg EM. Incidence and estimated need of caesarean section, inguinal hernia repair, and operation for strangulated hernia in rural Africa. *Br Med J* 1984; **289**: 92–3

Trauma centres and the efficient use of financial resources

Sir

Trauma is an emotive subject and despite evidence that up to 30 per cent of in-hospital deaths from trauma are potentially avoidable[1] there remains controversy and confusion to how best it can be improved This has been highlighted recently by O'Kelly and Westaby's timely article on support of the provision of a nationwide network of Trauma Centres (*Br J Surg* 1990; **77**. 1142–4). Why is it that the overall response to improving trauma care has been so muted? Although the establishment and recognition of accident and emergency as a separate specialty with its own well-defined career structure, followed more recently by the introduction of advanced trauma life support (ATLS) courses and paramedical ambulance training have gone some way towards improving trauma care, these are not enough The reasons would appear to be quite deep-seated and the medical profession, in particular the surgeons, must take some of the blame.

Locoregional trauma care, except in isolated centres of enthusiasm, is on the whole poorly organized, inadequately prepared and inappropriately staffed. Recent identification of severe defects in junior staffs' assessment of trauma priorities[2] must be acted upon swiftly There remains no structured training programme for trauma surgery, and few, if any, hospitals have a formal, consultant-led 'trauma team' Well-defined regional policies for the management of multiple-trauma patients do not exist in most centres and emergency radiology is not always readily available. Swift access to an operating theatre without having to break-in to a colleague's elective list is a luxury few surgeons have ever experienced.

How then, can we expect regional trauma centres to be commissioned throughout the country if we cannot improve and formalize our own locoregional services? Better care requires a multidisciplinary commitment involving staff at all levels of seniority, and must be accompanied by a structured training program and well-defined protocols of management There is no doubt that this work is particularly onerous for the emergency surgeon as it is high profile, high pressure and emotionally intense. However, the surgeon, with his regular exposure to shocked and critically injured patients, emergency surgery and nutritional supportive care, is the one most appropriately placed to take on the central co-ordinating role

However, if we wish to imrove trauma care, and there is little doubt there is ample room to do so, then it is up to the surgical specialties and accident and emergency staff to work more closely together Then, with a united front and evidence of a well organized locoregional system, we may go forward to demanding the provision of fully integrated trauma centres.

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1. Anderson ID, Woodford M, de Dombal TF, Irving M. Retrospective study of 1000 deaths from injury in England and Wales. *Br Med J* 1988, **296**. 1305–8
2. Wood PR, Foley MA, Peel WJ, Lawler PG. Junior medical staff and the assessment of trauma *Ann R Coll Surg Engl* 1990, **72**· 196–8.

Regional lymph node dissection for malignant melanoma

Sir

The importance of radical lymph node dissection for Stage II malignant melanoma has been emphasized by Jonk and coworkers (*Br J Surg* 1990; 77: 665–8) in their recent paper on patients in whom the primary lesion is undetectable or has undergone spontaneous regression. All of their patients with previous lymph node biopsy had residual tumour in the radical dissection specimens.

Patients presenting with cervical lymph node metastases had a significantly poorer survival than those with deposits in the groin or axilla. It was suggested that this might be due to undetected primaries in the scalp, although female patients (who are less inclined to lose hair and expose the scalp) generally fare better than males. Furthermore patients with documented regression of a primary lesion appear to have a prognosis similar to those in whom the primary was not found[1,2] while 'in transit' metastases do not significantly affect survival. It seems likely then that tumour cells in the lymph nodes contribute significantly to subsequent distant metastasis and death. The poorer survival following cervical block dissection may be due to the closer proximity of the nodes to the thoracic duct (facilitating secondary haematogenous spread) or the fact that significantly more lymphatic tissue is left behind in the form of occipital, pre- and postauricular and contralateral cervical nodes

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1 Milton GW, Shaw HM, McCarthy WH. Occult primary malignant melanoma: factors influencing survival. *Br J Surg* 1977; **64**: 805–8.

2 Reintgen DS, McCarty KS, Woodard B, Cox E, Siegler HF. Metastatic malignant melanoma with an unknown primary. *Surg Gynecol Obstet* 1983, **156**: 335–40.

Treatment of paraphimosis

Sir

It was with interest that I read the recent article by Hamdy and Hastie (*Br J Surg* 1990, 77: 1186) concerning their method of treatment of paraphimosis by direct and multiple needle puncture

For many years, however, I have employed a simpler, non-invasive, less alarming and, presumably, less painful method with consistent success, whilst never having had to resort to emergency dorsal slit or circumcision. The method requires.

1. A 50 ml vial of 50% dextrose solution
2. A sterile gauze swab
3. A degree of patience on behalf of surgeon and patient

On presentation the paraphimosis is simply wrapped in the gauze swab which has been liberally soaked in the hypertonic dextrose and left *in situ* for a period of at least 1 h. Following this the swelling has invariably reduced in size, the oedema having been dissipated by osmosis into the hypertonic solution Manual reduction is then easy, with only occasional recourse to the use of a penile local anaesthetic block or inhaled Entonox.

The method has other applications: on my suggestion my wife (herself a general practitioner) treated a 90-year-old woman's procidentia which although viable had become congested, oedematous and irreducible. Although the swelling took a little longer to dissipate, manual reduction was easily accomplished without necessity for hospital admission.

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Endoscopic transthoracic electrocautery of the sympathetic chain for palmar and axillary hyperhidrosis

Sir

I read with interest this article by Byrne *et al* (*Br J Surg* 1990, 77: 1046–9) particularly as I was taught the technique by one of Professor Hederman's proteges. From my experience of over 50 cases I would, however, make the following observations.

1. An experienced anaesthetist is required and the monitoring of vital functions must be frequent, as there can be sudden loss of cardiac filling due to mediastinal shift. We use continuous pulse oximetry. Bradycardia can occur due to the bilateral cardiac sympathectomy.

2. While I agree that it is easier to use a double puncture technique a much better cosmetic result is achieved by inserting the diathermy trocar into the anterior axillary line, one space below the laparoscope This hides the incision behind the breast fold in females

3 Compensatory hyperhidrosis is often a problem and it is important to resist the temptation to do both hands and feet, indeed, I have looked after one patient who had Smithwick's procedure (total sympathectomy by cervical,thoracic and lumbar operations) and whose compensatory hyperhidrosis on the buttocks is so severe that she appears to have been incontinent.

Nevertheless, despite these reservations endoscopic transthoracic cautery should be offered to more patients with hyperhidrosis and this message must be relayed to our dermatological colleagues.

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Book reviews

Current Surgical Diagnosis and Treatment

L. W Way 250 × 180 mm. Pp. 1282. Illustrated. 1990 East Norwalk Appleton and Lange. $39.95 softback.

The ninth edition of *Current Surgical Diagnosis and Treatment* is a credit to its authors and editor. It is a comprehensive introduction to surgery in the broader sense encompassing not only a review of surgical disease by organ system but including initial chapters devoted to general surgical and relevant medical topics. Surgical complications, special medical problems (including a section on the elderly patient), radiation therapy and the management of the injured patient are examples. Specialist surgical subjects, e.g. neurosurgery, otolaryngology and cardiac surgery are included in addition to accounts of oncology and organ transplantation. The text is clearly written and broken into short sections with relevant references conveniently interspersed through the chapters. Unfortunately, of necessity, there is a dearth of illustrations but such line drawings, radiographs and photographs as there are, are clearly presented

Modern imaging techniques are frequently discussed and I felt that a chapter dealing with the basic principles of some of the technical adjuncts to surgery, e.g. laser, fibreoptics cryosurgery and operating room theatre design would enhance the book.

This volume is not only instructive to final year srudents but also to surgeons in training, particularly those studying for the new FRCS examination. It must rank amongst the foremost of general surgical texts of the decade.

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Hereditary Cancer and Preventive Surgery

W. Weber, U Laffer, M Dürig, eds. 155 × 227 mm. Pp. 118 + x. Illustrated. 1990. Basel· Karger. £42.60 softback

The presentations of an international group of contributors to a Swiss cancer conference devoted to family cancer are presented in this book consisting of 16 chapters.

Contributions (many by distinguished authors) discuss hereditary cancer and preventive surgery, although often the distinction between prophylactic surgery for hereditary and sporadic cancer is blurred. The subjects of hereditary breast and colorectal cancer predominate although two chapters are devoted to skin melanomas and one to endocrine tumours. Some chapters report specific results whilst others contain an overall review of a subject. Genetic and surgical aspects of hereditary disease are sometimes discussed in depth but often in broad outline only. Screening protocols are recommended but there is no new information on their likely effectiveness or cost.

This book represents a timely reminder on the importance of inherited susceptibility to common cancers. Most surgeons will find this book of interest although some chapters will be less relevant to his or her specific practice than others.

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Radiation Enteritis

R. B. Galland and J Spencer, eds. 160 × 240 mm Pp. 266 Illustrated 1990. Sevenoaks Edward Arnold. £37 50 hardback.

Inspite of the wealth of knowledge that now exists about the causes and management of radiation induced bowel and bladder injuries, these injuries are still often badly managed, particularly of course by those who see them infrequently. In 1989 *Pelvic Radiation Disease* was published by Springer-Verlag and it brought together in a compact volume much information to help the postgraduate student or the clinician confronted with this uncommon but increasing problem Now *Radiation Enteritis* has appeared and is a far better buy. Comparison of the two books shows immediately the greater depth and confidence of this newer volume, and this may be partly because *Pelvic Radiation Disease*, although multi-author, restricted itself to authors from a single centre in this country, whereas the new work calls on experts across both this country and the USA.

This book covers its subject in depth which includes the history, pathology, and radiology as well as methods of prevention and the medical and surgical managment, summarizing virtually all that is currently known about the subject and including a wealth of references What is particularly successful is the way it sets out clear general principles, and then supports these with detailed practical advice on managment. All this makes the book considerably larger than its earlier-published rival and yet at £37.50 it is £12 cheaper.

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Current Surgical Practice. Volume 5

M Hobsley, J. Hadfield, T Treasure 155 × 233 mm Pp. 314 Illustrated. 1990 Sevenoaks Edward Arnold £24.50 softback

The original concept of this series was to present the topics covered in lectures at the Royal College of Surgeons of England to a wider audience. Devotees have come to expect matters of the moment to be addressed in an authoritative yet individualistic way They will not be disappointed with Volume 5 which embraces subjects from the mouth to the nether regions tackled by acknowledged experts, largely home grown but including contributers from Australia, France and India

There are also innovations in this volume. A section of nine chapters is devoted to iatrogenic surgical disease Injury to nerves, the spinal cord, bile ducts, ureter, the saphenofemoral junction as well as damage resulting from the bandaging and splinting are all covered The common pitfalls are highlighted and remedies suggested where possible This is worthwhile reading for all surgeons from all specialties

In 1976 in the first edition John Hadfield wrote on benign diseases of the breast. In the fifth he considers advances in our understanding of this subject. He should be well satisfied that on his retirement as joint editor, current surgical practice is as a vehicle for documenting such advances across the whole field of surgical endeavour, and on this the reputation of these volumes has come to rest

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Notices and announcements

25–26 March 1991
Injury Research Group Meeting
Newcastle upon Tyne, UK
Information. Dr R. N. Barton, North Western Injury Research Centre, Stopford Building, University of Manchester, Oxford Road, Manchester M13 9PT, UK

3–5 April 1991
Annual Meeting of the Association of Surgeons of Great Britain and Ireland
Oxford, UK
Information: Honorary Secretary, Association of Surgeons of Great Britain and Ireland, 35/43 Lincoln's Inn Fields, London WC2A 3PN, UK

11–12 April 1991
4th International Benign Breast Disease Symposium
Manchester, UK
Information: Professor R. E. Mansel, University Hospital of South Manchester, Nell Lane, West Didsbury, Manchester M20 8LR, UK

17–19 April 1991
International Conference on Railway Suicide
London, UK
Information: Professor R. Farmer, Charing Cross and Westminster Medical School, 17 Horseferry Road, London SW1P 2AR, UK

17–20 April 1991
Kocher Symposium: Endocrine Surgery
Berne, Switzerland
Information. Mr K. Schluep, Johnson and Johnson AG, Rotzenbühlstrasse 55, CH-8957 Spreitenbach, Switzerland

18–21 April 1991
SAGES 1991 Scientific Session
California, USA
Information. Program Committee, SAGES, Suite 409, 1271 Stoner Avenue, Los Angeles, CA 90025, USA

22–25 April 1991
4th International Symposium on Cardiovascular Pharmacotherapy
Geneva, Switzerland
Information: ISCP'91, c/o AKM Congress Service, PO Box CH-4005, Basel, Switzerland

3 May 1991
Somatostatin '91 and Other Peptide Analogues
Leicester, UK
Information: Mr P. K. Donnelly, Department of Surgery, Leicester General Hospital, Gwendolen Road, Leicester LE 5 4PW, UK

4–5 May 1991
5th International Meeting of the Australian and New Zealand Society of Phlebology
Sydney, Australia
Information: Dr G Mark Malouf, Secretary, ANZ Society of Phlebology, PO Box 2166, North Parramatta 2151, Sydney, Australia

8–10 May 1991
Blood Vessel Imaging Using Ultrasound Techniques
Torquay, UK
Information: Mr K. N. Humphries, 10 Swale Drive, Chandlers Ford, Hampshire SO5 3QY, UK

8–11 May 1991
Melanoma '91, Brighton International Melanoma Conference
Brighton, UK
Information. Dr N. Kirkham, Department of Histopathology, Royal Sussex County Hospital, Brighton BN2 5BE, UK

8–11 May 1991
XXVIth Congress of the European Society for Surgical Research and the VIIIth Tripartate Meeting of The Surgical Research Society and The Society of University Surgeons
Salzburg, Austria
Information ESSR Congress Office, 1st Surgical Department, Landeskrankenanstalten, Mullner Hauptstrasse 48, A-5020 Salzburg, Austria

15–18 May 1991
Annual Meeting of the American Association for Cancer Research
Houston, Texas, USA
Information: American Association for Cancer Research, Public Ledger Building, Suite 816, Sixth and Chestnut Streets, Philadelphia, PA 19106, USA

17 May 1991
British Association for Endocrine Surgeons
Cambridge, UK
Information: Mr A. W. Goode, Surgical Unit, 4th Floor Alex Wing, The Royal London, London E1 1BB, UK

20–24 May 1991
Pacific Association of Paediatric Surgeons 24th Annual Meeting
Hong Kong
Information Secretariat, PAPS Hong Kong, Department of Surgery, University of Hong Kong, Queen Mary Hospital, Hong Kong

30 May–1 June 1991
4th International Symposium on the Biology, Immunology and Surgery of the Greater Omentum
The Netherlands
Information: Secretariat, 4th International Omentum Symposium, Mrs W. J Buys–Utrecht Cancer Research Centre, Servaasbolwerk 14, 3512 NK Utrecht, The Netherlands

June 1991
33rd Annual Meeting of the International College of Angiology
Singapore
Information: International College of Angiology, 1044 Northern Blvd, Ste 103, Roslyn, New York 11576, USA

2–14 June 1991
Methods of Immunologic Research and Diagnosis
Buffalo, New York, USA
Information: James F Mohn, Director, The Ernest Witebsky Center for Immunology, 272 Sherman Hall, Buffalo, New York 14214, USA

6–8 June 1991
5th European Congress of the Society for Surgery of the Shoulder and the Elbow
Wurzburg, FRG
Information. Prof. Dr. med. J. Eulert, Orthpadische Universitatsklinik, Konig-Ludwig-Haus, Brettreichstr. 11, 8700 Wursburg, FRG

9–12 June 1991
Fifth International Conference on Malignant Lymphoma
Lugano, Switzerland
Information: F. Cavalli, Division of Oncology, Ospedale San Giovanni, 6500 Bellinzona, Switzerland

11–13 July 1991
XVIth International Update on Liver Disease
London, UK
Information Professor Neil McIntyre, Academic Department of Medicine, Royal Free Hospital, Pond Street, London NW3 2QG, UK

14–16 July 1991
Techniques in Pulmonary and Oesophageal Surgery
Liverpool, UK
Information Mr R. J. Donnell, Cardiothoracic Centre, Broadgreen Hospital, Thomas Drive, Liverpool L14 3LB, UK

25–31 August 1991
International Surgical Week
Stockholm, Sweden
Information Scientific Secretariat, 155, Hauptstrasse 63, PO Box 411, CH-4153, Reinach BL1, Switzerland

1–6 September 1991
6th World Congress in Ultrasound
Copenhagen, Denmark
Information Spadville Congress Service, Sommervaj 3, DK-3100 Hornbaek, Denmark

7–10 October 1991
5th Congress of the European Society for Organ Transplantation
Maastricht, The Netherlands
Information: 5th ESOT Congress, Conference Agency Limburg, University Hospital Limburg, PO Box 1918, 6201 BX Maastricht, The Netherlands

7–9 November 1991
3rd Combined Meeting of the Nederlandse Vereniging voor Thoraxchirurgie and the Deutsche Gesellschaft für Thorax-, Herz- und Gefässchirurgie
Maastricht, The Netherlands
Information: Organizing Secretariat, Conference Agency Limburg, University Hospital Maastricht, PO Box 1918, 6201 BX Maastricht, The Netherlands

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OFFICIAL PUBLICATION OF
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The North Pacific Surgical Association
The Society for Clinical Vascular Surgery
The Society of Head and Neck Surgeons
The Southwestern Surgical Congress
The Association for Surgical Education

Contents

Papers of the Society for Surgery of the Alimentary Tract

PRESIDENTIAL ADDRESS

2 **The Consumption of Our Heritage**
David L. Nahrwold

STATE-OF-THE-ART ADDRESS

6 **Humoral Control of Gut Function**
James C. Thompson

SCIENTIFIC PAPERS

19 **A Prospective Longitudinal Study of Observation Versus Surgical Intervention in the Management of Necrotizing Pancreatitis**
Edward L. Bradley III and Keith Allen

26 **Implications of Peritoneal Cytology for Staging of Early Pancreatic Cancer**
Andrew L. Warshaw

31 **Erythromycin Enhances Delayed Gastric Emptying in Dogs after Roux-Y Antrectomy**
Robert G. Carlson, Michael P. Hocking, Kenneth R. Courington, Charles A. Sninsky, and Stephen B. Vogel

36 **Laparoscopic Guided Cholecystectomy**
Karl A. Zucker, Robert W. Bailey, Thomas R. Gadacz, and Anthony L. Imbembo

45 **Are Pancreatoenteric Anastomoses Improved by Duct-to-Mucosa Sutures?**
Barry S. Greene, Jean M. Loubeau, James B. Peoples, and Dan W. Elliott

51 **Clenbuterol Plus Acivicin Decrease Tumor Growth and Increase Muscle Mass in Rats Maintained on Total Parenteral Nutrition**
William T. Chance, Lequn Cao, Fu-sheng Zhang, and Josef E. Fischer

57 **Differential Diagnosis of Sclerosing Cholangiocarcinomas of the Common Hepatic Duct (Klatskin Tumors)**
L. Albert Wetter, Ernest J. Ring, Carlos A. Pellegrini, and Lawrence W. Way

64 **Proximal Gastric Vagotomy in the Emergency Treatment of Bleeding Duodenal Ulcer**
Brent W. Miedema, Paul R. Torres, Michael B. Farnell, Jon A. van Heerden, and Keith A. Kelly

69 **A 27-Year Experience with Splenectomy for Gaucher's Disease**
Phillip R. Fleshner, Arthur H. Aufses, Jr., Gregory A. Grabowski, and Richard Elias

76 **Vascular Complications After Orthotopic Liver Transplantation**
Alan N. Langnas, Wagner Marujo, Robert J. Stratta, R. Patrick Wood, and Byers W. Shaw, Jr.

84 **Pancreatic Regeneration After Partial Pancreatectomy**
Dilipkumar Parekh, Courtney M. Townsend, Jr., Srinivasan Rajaraman, Jin Ishizuka, and James C. Thompson

90 **Manometric and Functional Comparison of Ileal Pouch Anal Anastomosis With and Without Anal Manipulation**
Wayne Tuckson, Ian Lavery, Victor Fazio, John Oakley, James Church, and Jeffrey Milsom

97 **High-Grade Dysplasia in the Columnar-Lined Esophagus**
Nasser K. Altorki, Masakatsu Sunagawa, Alex G. Little, and David B. Skinner

101 **A Critical Analysis of the Largest Reported Mass Fecal Occult Blood Screening Program in the United States**
Jon B. Morris, Thomas A. Stellato, Barbara B. Guy, Nahida H. Gordon, and Nathan A. Berger

107 **Somatostatin Analogue Treatment Inhibits Post-Resectional Adaptation of the Small Bowel in Rats**
Barbara L. Bass, Beverly A. Fischer, Carla Richardson, and John W. Harmon

113 **Surgical Management of Nonparasitic Cystic Liver Disease**
Herminio Sanchez, Michel Gagner, Ricardo L. Rossi, Roger L. Jenkins, W. David Lewis, J. Lawrence Munson, and John W. Braasch

120 **Factors Influencing Survival After Pancreaticoduodenectomy for Pancreatic Cancer**
John L. Cameron, David W. Crist, James V. Sitzmann, Ralph H. Hruban, John K. Boitnott, Alexander J. Seidler, and JoAnn Coleman

126 **Mediators of Bile Acid-Induced Alterations in Gastric Mucosal Blood Flow**
Wallace P. Ritchie, Jr., and David Mercer

131 **Quantitative Analysis of Portal Tract Infiltrate Allows for Accurate Determination of Hepatic Allograft Rejection**
Howard Sankary, Preston Foster, Ken Novich, Marylin Ashmann, A. Bhattacharyya, James Coleman, and James Williams

136 **Prospective, Randomized Trial of the Biofragmentable Anastomosis Ring**
Melvin P. Bubrick, Marvin L. Corman, C. Joseph Cahill, Thomas G. Hardy, Jr., F. Carter Nance, Clayton H. Shatney, and the BAR Investigational Group

144 **Effect of Enteral Nutrition on Exocrine Pancreatic Function**
Gyorgy Bodoky, Laszlo Harsanyi, Akos Pap, Tibor Tihanyi, and Lajos Flautner

149 **Glucose Intolerance and Hyperinsulinemia of Cirrhosis Are Not Results of Spontaneous or Surgical Portosystemic Shunting**
Kenneth R. Sirinek, Thomas M. O'Dorisio, and Barry A. Levine

154 **Long-Term Studies of Mental Health After the Greenville Gastric Bypass Operation for Morbid Obesity**
Gregory S. Waters, Walter J. Pories, Melvin S. Swanson, Helen D. Meelheim, Edward G. Flickinger, and Harold J. May

159 **Prospective Study of a Prosthetic H-Graft Portacaval Shunt**
Alexander S. Rosemurgy, Earl W. McAllister, and Robert E. Kearney

165 **Tachykinins in the Canine Gastroesophageal Junction**
Anthony D. Sandler, James W. Maher, Joel V. Weinstock, Charles D. Schmidt, Jerry F. Schlegel, Jean Y. Jew, and Terrance H. Williams

171 **Immunophenotyping in the Management of Gastric Lymphoma**
Hugo V. Villar, Randolph Wong, Benjamin Paz, David Bull, Leigh Neumayer, Thomas Grogan, and Catherine Spier

177 **Why Does Somatostatin Cause Gallstones?**
Steven A. Ahrendt, Gretchen E. McGuire, Henry A. Pitt, and Keith D. Lillemoe

184 **The Liver Plays an Important Role in the Regulation of Somatostatin-14 in the Rat**
Steven E. Raper, Piyush C. Kothary, Norihiro Kokudo, John DelValle, and Frederic E. Eckhauser

A17 **Information for Authors**
A21 **Classified Advertising**
A22 **Classified Advertising**

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Br. J. Surg. 1991, Vol. 78, June, 641–642

Professor D. C. Carter and Mr R. C. G. Russell

Mr Christopher Russell and Professor David Carter retired from their posts as joint Editors of *The British Journal of Surgery* in April this year and it is appropriate that they should be thanked for their hard work on behalf of the *Journal* in this issue, as the manuscripts which were selected by their editorial team will have been published by July.

It is an indication of their hard work and dedication that the editorial team needed further expansion following their retirement to cope with the current and predicted future workload. The *Journal* now has a Senior Editor, Professor Robin Williamson, Professor John Farndon has become the Editor, Mr John Murie has taken on the role of Review Editor and Mr Colin Johnson is the new Associate Editor.

Christopher Russell

Hey Groves, the first Editor of *The British Journal of Surgery*, served for 28 years until he was forced to retire by ill health 'aggravated by enemy action'. The second Editor, Sir Cecil Wakely, served for 30 years. Mr Felix Eastcott and I, sensibly, resigned after much shorter periods but Chris Russell has been involved with the editorial process of *The British Journal of Surgery* since 1978, firstly as Associate Editor and then as Editor.

Chris, more than anyone else in the editorial team, has been responsible for the enormous changes in the *Journal* over the last 13 years and for its rise in international stature. He is a tireless perfectionist who has been totally unstinting of himself and his time in his service to the *Journal*. Publishing a monthly scientific journal is a remorseless task; an average weekend's reading might involve 70 to 80 manuscripts and this work has increased every year that he has been involved in the affairs of the *Journal*. As the *Journal* has grown he has instituted considerable improvements and changes in the editorial process, which have all been directed towards quality control. Though no editorial machinery is foolproof the standard of presentation and the accuracy of manuscripts has increased considerably, in spite of the fact that a far larger percentage of papers published in *The British Journal of Surgery* now originate from overseas, and are frequently from authors whose first language is not English. *The British Journal of Surgery*, in spite of its name, is a very international journal and Chris Russell has been, to a great degree, responsible for its international standing.

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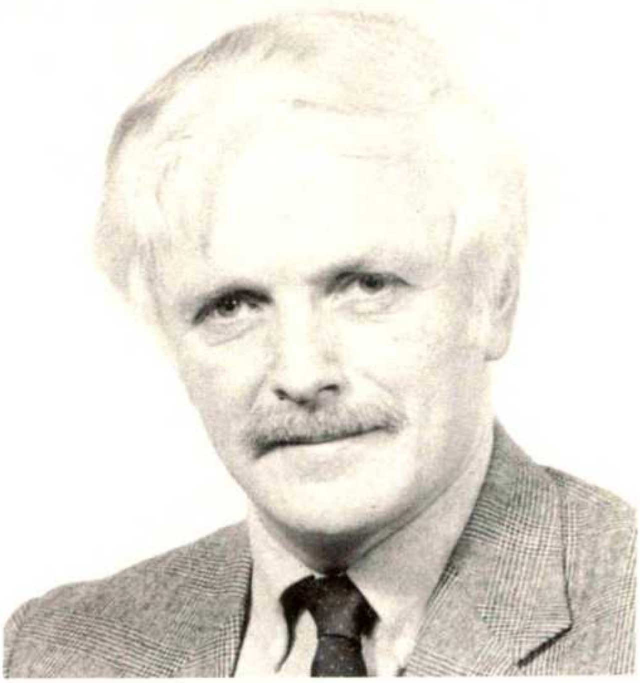
David Carter



David Carter has, in addition to sharing the role of Editor in the selection of manuscripts, adopted the role of Review Editor and achieved considerable success in improving the standard of reviews published in *The British Journal of Surgery* and in expanding our publication of leading articles. It is extremely difficult to achieve an overall high standard of reviews in a journal and we have in general abandoned invited reviews, substituting proffered reviews which attract a fee if accepted but have the advantage for the editorial team that they can also be rejected. It is a reflection on David Carter's tact and diplomacy, and his wide circle of internationally renowned acquaintances, that the standard of reviews and leading articles has increased to such a degree, bringing new vitality to the *Journal*.

David Carter has a wry sense of humour and a vast fund of common sense. I am, personally, particularly grateful that he has accepted the invitation of the Officers of The British Journal of Surgery Society to succeed Professor Robin Williamson as the Society's Treasurer and that his wise counsel will not be lost to the *Journal*.

The Officers of The British Journal of Surgery Society would like to thank both David Carter and Chris Russell very much, on behalf of all the *Journal*'s subscribers, for their excellent work and convey our good wishes to the new editorial team, who have a hard act to follow.

C. W. Jamieson

Chairman
The British Journal of Surgery Society

Br. J. Surg. 1991, Vol. 78, June, 643–645

Angioplasty for mild intermittent claudication

Intermittent claudication occurs in more than 5 per cent of the population over 55 years of age[1]. The cause is almost always atherosclerosis, and the offending lesions are usually found in the superficial femoral and iliac arteries[2]. The progression of claudication varies; some patients may improve in the early stages, but of those referred to outpatient departments, two-thirds will continue to deteriorate over the next 2–3 years[3]. After 5 years, 7 per cent will require amputation for intractible rest pain, ulceration and gangrene[2].

At present, treatment for peripheral vascular disease is restricted mainly to reconstructive surgery or angioplasty for severe claudication or a critically ischaemic limb threatened with amputation. Mild claudication, in which the patient can walk free of pain for over 200 metres, does not generally merit reconstructive surgery because the discomfort and restriction in lifestyle are not considered severe enough to justify the surgical risks. Such patients may be offered drug therapy, but often there is little to be done other than 'stop smoking and keep walking'[4].

Percutaneous transluminal angioplasty (PTA) may offer hope to these patients with mild claudication. PTA was conceived over 25 years ago[5], but the technique underwent considerable modification[6] before being widely introduced into clinical practice in the early 1980s. Since then, use has increased dramatically. In patients with short iliac and femoropopliteal occlusions, the results are comparable with reconstructive surgery, but with the advantage of a lower mortality and complication rate[7]. More than 90 per cent of stenoses can now be successfully dilated in experienced hands[8]. Use of PTA in claudicants is still largely restricted to patients with severe symptoms who might otherwise have had reconstructive surgery. Increasingly, however, vascular specialists are being pressed to alter this cautious approach and to treat milder claudication by PTA. However, this could be a classic example of new technology being adopted and accepted without challenge and before thorough evaluation, because there is still a lack of evidence regarding the long-term benefits of the technique.

The procedure is not without risk, and this may account partly for reluctance to intervene in patients with mild claudication. The most frequent complication, in 5 per cent of cases, is haematoma around the puncture site. More severe complications requiring surgical intervention are rare – 0·7 per cent if claudication is the only symptom[9]. Limb loss is exceedingly uncommon, involving around 0·1 per cent of those with severe disease[9]. However, improvements in technique and the design of materials have probably reduced the number of patients needing surgery to rectify complications. In cases of early disease, where the procedure is often technically easier, the risks may well be lower[9]. Nevertheless, there should be surgical back-up, even for straightforward cases.

In early claudication the usual lesion is a stenosis or short length occlusion in the superficial femoral artery. Such lesions are technically amenable to angioplasty. In more advanced claudication where the entire superficial femoral artery has occluded, the lesion is often beyond treatment by angioplasty. Thus in early claudication there may be a 'window of opportunity' for non-surgical treatment which could be lost as the disease progresses, leaving surgical reconstruction as the only alternative.

PTA is not cheap (around £300 per procedure for materials alone). However, the cost of initial treatment might be recoverable if PTA offered a better chance of long term patency than conservative treatment. The initial cost might then be offset by long term savings on expensive reconstructive surgery. This potential saving must be balanced by the cost of repeat dilatations in some patients. Thus the net financial effect is difficult to estimate.

The patient derives immediate benefit from PTA in terms of walking distance. Although supervised intensive walking therapy may produce better results over a period of one year[10], this supervision may not be available in many UK hospitals. Also, the long term potential for much greater walking distance after PTA is reflected in the significantly improved ankle pressures compared with walking therapy.

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However, it is uncertain whether long term prognosis for the limb is improved after PTA. Atheroma could be accelerated after restoration of flow, as disease has been shown to advance more rapidly with sub-critical than critical narrowing[11]. On the other hand, clinical deterioration has been found to be worse in patients with occlusion than stenosis[12], and thus preservation of vessel patency by PTA might be advantageous.

Patients with claudication have a mortality which is about two to three times that of an age and sex matched population, and around half the deaths are attributable to ischaemic heart disease[13]. It might be possible to reduce this high mortality if a change in lifestyle of patients with claudication could be brought about. The patient may be able to achieve such a change after PTA by returning quickly to brisk walking, thus engaging in a beneficial form of exercise[14], with minimal risk from such levels of exertion. On the contrary, such exercise is protective against death from coronary artery disease[15]. It is important, therefore, that the clinician should be aware of potential benefits to health in general when treating claudication.

Motivation alone is also an important factor. An all too familiar picture is the vicious circle of exercise restriction, weight increase, depression and smoking leading in turn to further exercise limitation and further vascular events. Rapid relief of claudication offers a break in this circle. Additional medical benefits might therefore include greater motivation to stop smoking, and better control of body-weight.

It is also easy to overlook the extent of disability. For the patient suffering even mild claudication, a return to normal activities of daily living such as walking to the shops, exercising the dog or simply walking for its own sake is far from a mundane consideration, and the resumption of these activities may provide a new lease of life with consequent psychological and health benefits. The vascular specialist is sympathetic to such needs and might very reasonably opt to treat by PTA in order to achieve rapid results. However, enthusiasm to alleviate disability in this way must be tempered by careful consideration of the potential long term problems.

In summary, percutaneous transluminal angioplasty is being employed on a large and increasing scale. It is a relatively minor procedure which may carry substantial benefits far beyond simple relief of leg symptoms, but has been subjected to little objective evaluation. There is, therefore, an urgent need for randomized controlled trials of PTA, particularly in the more controversial setting of patients with mild claudication, to assess both short and long term benefits, including quality of life.

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Announcement

All readers should remember that, since January 21, the editorial office of *The British Journal of Surgery* has had a new address. All correspondence should now be addressed to:

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Correspondents who have written to our previous address in Guildford should not, however, be concerned. Butterworth–Heinemann Ltd. still has an office there and all mail will be quickly rerouted.

Br. J. Surg. 1991, Vol. 78, June, 646–647

Invasive breast cancer – where now?

The management of breast cancer is undergoing great change, as is indicated in recent updates[1,2]. This has been prompted by the knowledge that, once invasive, the disease disseminates quickly making the treatment of micrometastatic disease an equal if not greater issue than treatment of the local tumour.

For most women, breast cancer is still a symptomatic condition, presenting as a hard and often tethered lump in the breast. The majority of patients with symptomatic disease already have micrometastases although it may be many years before these cause clinical relapse. Only some 25 per cent remain free of disease for the rest of their life. The reports of the Early Breast Cancer Trials Collaborative Group (the most recent still unpublished) have firmly established that systemic treatment of symptomatic breast cancer with antioestrogens or cytotoxic drugs, when given as an adjuvant to local surgery or radiotherapy, reduces mortality by 20 per cent. Although statistically of great significance, the absolute gain in survival over that of control patients is only 6–7 per cent at 5 years. This differential can be improved only by more effective systemic treatment such as dose-intense regimes of chemotherapy supported by leucovorin, colony stimulating factors and autologous marrow transplantation or by better methods of selecting treatment appropriate to the patient's disease. Currently, aggressive chemotherapy is likely to be acceptable only for aggressive cancers; therefore it is important to be able to identify individual patients with a high chance of relapse.

It is generally agreed that tumours greater than 2 cm in size, and those associated with involved axillary lymph nodes are relatively 'bad'. Obviously involvement of axillary nodes indicates the likelihood of micrometastases elsewhere but not all those with large tumours or involved nodes relapse quickly; there are subsets of both with an uncommonly good prognosis. Thus, no less than 21 of 81 20-year survivors in the East Anglia study had positive axillary lymph nodes at the time of primary local treatment[3]. The converse is equally true. Small tumours and those without axillary node involvement may still relapse rapidly.

There are a number of measurable tumour factors which give some guidance to the biological nature of the disease. These relate to the degree of differentiation: the better differentiated the less aggressive the tumour is likely to be. Markers of differentiation include histological type, cell and nuclear grade, elastosis and oestrogen receptor status. Some of these have been combined with size and node status to provide 'predictive indices' which relate well to prognosis, but only in a statistical sense, by defining groups of patients with different probabilities of relapse. Within each group there must still be considerable variation of behaviour. The definition of such indices requires that the tumour is removed and the axilla dissected. The discriminating power of sophisticated tumour markers, such as growth factor receptors, homologous oncogenes and genes associated with invasion and its suppression, is being explored. It is hoped that their use may eventually provide a simple, more reliable and less invasive means of determining prognosis for the individual; particularly attractive is the possibility that they could be assayed on cellular aspirates.

Many medical oncologists believe that the objective in treating micrometastatic disease is to achieve cell-kill by cytotoxic chemotherapy. Others consider this approach too radical, knowing that suppression of growth with tamoxifen is relatively free of morbidity and therefore more acceptable to patients. But tamoxifen can only benefit those with sensitive disease and this cannot be determined on an individual basis by *in-vitro* tests; nor can we tell if the denial of chemotherapy is reducing the chance of cure.

One way to determine the effectiveness of both antioestrogen and cytotoxic systemic treatment in an individual patient is to use her primary tumour as a biological indicator of response, delaying local therapy until tumour sensitivity is known. Accepting the assumption that the effect of systemic treatment on the primary tumour mirrors the effect on micrometastases, it is logical to leave the primary tumour *in-situ* at least until maximal regression has been achieved. Now that a precise diagnosis

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can be made by fine-needle aspiration cytology, this approach can be applied to operable as well as to locally advanced disease. This emphasis on systemic therapy has reinforced the essential aim of local treatment, namely to control local disease, and has strengthened the realization that this can be achieved without sacrificing the breast. For success, breast conserving therapy requires that the surgeon, radiologist, radiotherapist and pathologist collaborate closely, that strict selection criteria are defined, and that these are adhered to.

Mammographic screening has presented surgeons with a different form of invasive breast cancer from that seen in the symptomatic clinic, this being in a preclinical asymptomatic phase. Such tumours are small and likely to be more differentiated than those which present symptomatically and are therefore less likely to have micrometastic disease in the axilla or elsewhere. Again, there is great variation of behaviour, some tumours being aggressive and leading to early relapse. The recent report of the Advisory Committee on Breast Screening supports earlier findings that the treatment of invasive cancer at this early stage confers greater benefit than when applied later in the course of the disease. The Committee's analysis of available trials indicates that by the end of this century the current screening programme should prevent 1250 breast cancer deaths each year in the UK and suggests that each of the women will live for on average 20 years more[4].

It is the practice in some parts of Sweden to treat these small tumours by local excision alone[5]. However, confirmation of the safety of this approach can come only from controlled randomized trials such as are now being conducted in several countries. As it could lead to a saving in radiotherapy resource it is essential that this question be answered. Yet we know that in the UK only a small proportion of eligible patients are being considered for inclusion in such trials.

Whenever possible, a cytological diagnosis of cancer should be sought preoperatively, this by the use of sterotaxic fine-needle aspiration. An operation for cancer, rather than diagnostic biopsy, then can be planned as the first surgical procedure for asymptomatic disease.

It is obvious that although progress is being made in our understanding of what is required we still do not know the best treatment for the individual patient with invasive breast cancer. In most American States it is now a statutory obligation to explain all available options of treatment to those with breast cancer who then are expected to participate in the decision-making process. This opportunity should exist without legal enforcement, allowing patients to become fully informed about the problems which face a surgeon in providing the best advice. We have not yet reached the stage in the UK in which women have sufficient knowledge to participate in or seek information about ongoing trials. Hopefully this will come soon.

The current UK trial of the treatment of screen-detected carcinoma *in-situ* is the first national trial of the management of breast cancer to be carried out in this country. Similar initiatives are being explored for screen-detected and symptomatic invasive cancers and the rewards could be great, but only if there is support from surgeons and collaboration between trial centres.

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648–650

Influence of local recurrence on survival: a controversy reviewed from the perspective of soft tissue sarcoma

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The relationship between local recurrence and survival has been examined using the example of soft tissue sarcomas of the extremities. Studies that appear to indicate that local recurrence does not jeopardize survival are shown to have been inappropriately analysed, to have inadequate patient numbers, or both. A survival deficit due to local tumour recurrence cannot be excluded on present data, and clinical decisions regarding conservative versus *radical surgery will therefore continue to involve an element of value judgement.*

One of the most controversial issues in surgical oncology today is the relationship between local recurrence and survival. For some tumours, such as carcinomas around the head and neck or pelvis, local recurrence has an obvious impact on survival by virtue of local involvement of vital structures. For other tumours, such as breast cancer, malignant melanoma or malignant tumours of the limbs, local recurrence seldom has direct lethal consequences but nevertheless could influence survival if it resulted in an increased chance of distant metastasis.

This issue has considerable clinical importance, particularly in the management of patients with soft tissue sarcomas of the extremities. Limb-sparing combined modality treatment for these tumours appears to be associated with a higher incidence of local recurrence than does primary amputation[1,2]. A number of authors consider that patients having such local recurrence have an increased risk of metastatic disease and death[3–10], while others consider that the appearance of systemic disease is independent of local recurrence, and that local disease can usually be satisfactorily salvaged without impairment of survival[11–13]. Indeed, the different primary amputation rates in series reporting the management of soft tissue sarcoma probably reflect these different philosophies[6,8,14–18]. In this paper we review the methods used to determine the relationship between local recurrence and survival for soft tissue sarcomas, because the rate of local recurrence is relatively high and the cosmetic and functional implications of major amputation are substantial.

Assessing the outcome of salvage treatment

The simplest method of ascertaining the effect of local recurrence on survival is to examine the outcome of those patients who have developed locally recurrent disease, and compare it with those who have not. For example, Abbas *et al.*[11] studied 251 patients with soft tissue sarcomas at various sites and found that 5 and 10 year survival rates following treatment of 72 patients with local recurrence (excluding patients with simultaneous distant metastases) were 43 per cent and 33 per cent respectively. This compared favourably with 5 and 10 year survival rates for the whole group of 45 per cent and 30 per cent respectively, and the authors concluded that local recurrence was a potentially curable disease. Conversely, Owens *et al*.[5] in a study of 82 distal extremity sarcomas noted that four out of five patients with locally recurrent high grade tumour died, and concluded that local recurrence must therefore have 'grave prognostic import'. Unfortunately, since patients with locally recurrent disease are a highly selected group and no attempts have been made to stratify them according to other known risk factors, conclusions regarding the influence of local recurrence on survival from studies such as these are not valid.

A slight improvement in this method of analysis can be made by examining survival from the date of diagnosis rather than from the date of local recurrence, comparing cases with and without local recurrence at any time. For example Cantin *et al.*[4] in an influential paper from the Memorial Sloan–Kettering Cancer Center, noted that for soft tissue sarcomas of the trunk or extremity the probability of dying was increased twofold for patients developing a local recurrence compared with those who did not have a recurrence. Similarly, Markhede *et al.* from Sweden[3] and Bramwell *et al* from Manchester[16] have constructed survival curves for patients with and without local recurrence and noted that overall survival was impaired in the local recurrence group. Conversely, Rantokokko and Ekfors[2] found that the survival of 102 sarcoma patients having a local recurrence was no different from the group of 241 as a whole. Once again, conclusions regarding the association between local recurrence and impaired survival from this type of survival analysis require caution, since the two groups are selected and not strictly comparable. For example, the 'no recurrence' group is unfavourably weighted by all those patients who have died within a short time of diagnosis and before local recurrence has had a chance to develop. This anomaly can be compensated for by taking a landmark date of (say) 2 years, by which time the majority of local recurrences should have occurred. Patients dying within 2 years of diagnosis are thus excluded from the analysis and a statistically more satisfactory survival curve can be drawn. Collin *et al.*[8] have demonstrated a significant difference in overall survival between patients with and without local recurrence using this method, with 5 year survival rates of approximately 70 per cent and 90 per cent respectively.

A further major objection to all of these analyses is that the demonstration of an apparent relationship between local recurrence and survival could be due to a separate common prognostic factor. The development of local recurrence and distant recurrence could both be parallel manifestations of this common underlying risk factor. The above analyses are flawed because they address a multivariate problem with univariate methodology.

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Multivariate analyses of risk factors for survival

A more appropriate method of examining the relationship between local recurrence and survival is therefore to look at local recurrence as a risk factor for impaired survival by means of multivariate analysis. This takes into account other and possibly interrelated risk factors, and may elucidate whether any observed relationship between recurrence and survival is independent of the other variables.

The Memorial Sloan–Kettering group tackled this problem in a multivariate analysis of risk factors for survival in 423 patients with localized extremity soft tissue sarcomas[9]. Risk factors significantly associated with impaired overall survival were: pain as a local symptom on presentation, age over 53 years, high grade, proximal site, size > 10 cm, positive regional nodes, surgery by amputation, and inadequate surgical margins. Local recurrence was also examined as a risk factor; although it had emerged as significantly associated with overall survival on univariate analysis, the association was lost on multivariate analysis.

The link between inadequate surgical margins and survival in this study is of interest, and at first glance could be thought to imply that poor initial surgery leads to residual microscopic disease, local recurrence and distant failure. This is not necessarily the case, since a complex factor such as surgical margin may be the product of multiple other risk factors including some which have not been examined. The fact that bulky, proximal tumours may be difficult to excise with a clear margin is allowed for by including size and site among the variables studied. There may, however, be other important factors associated with resectability, which if included might show that margins were not independent risk factors. Similarly amputation itself may not be what leads to reduced survival (unless patients are dying of operative complications); tumours advanced enough to demand amputation may have other poor prognostic features in addition to size, site, grade and symptoms. The authors concluded from this study that local recurrence was 'associated with a significantly reduced survival', but the opposite point of view could equally well be taken from their data[9].

An improved method of examining local recurrence within a multivariate analysis makes allowance for the fact that local recurrence is a time-dependent factor, that is it occurs at a variable interval after the date of primary treatment[19]. This method of analysis recognizes that patients can be classified in both the recurrence-free and recurrence groups at different times during follow-up. The hazard ratio between the recurrence and recurrence-free groups then expresses the increased probability of dying at any paticular time during follow-up of those patients who have recurrence compared with those who have not. Using this methodology, a significant correlation has been found between local recurrence and survival for limb and limb girdle sarcomas by Stotter *et al*[20]. A similar result has also been reported by Emrich *et al.*[21] for high grade sarcomas at various sites.

While multivariate analyses can yield invaluable information concerning factors related to survival, a confident assertion about the influence of a complex factor such as local recurrence remains difficult and requires a large number of 'events' notably large patient groups, long follow-up, and large numbers of recurrences and deaths. Furthermore, a demonstrated association with prognosis does not prove a causal link since recurrence could be an expression rather than a determinant of poor prognosis.

Survival and controlled randomized trials

The third and statistically most satisfactory method of looking at the effect of recurrence on survival is to examine the relationship in the context of a prospective randomized trial. The effect of local recurrence can be studied if one arm of the trial has a higher local recurrence rate than the other and the treatment being studied is a local one (rather than systemic) which would not be expected *per se* to influence systemic disease and survival.

A good example is the prospective randomized trial of limb conserving surgery and radiotherapy versus amputation undertaken by the National Cancer Institute (NCI). Twenty-seven patients with high grade extremity soft tissue sarcomas were randomized to limb conservation and 16 to amputation. Both groups received adjuvant chemotherapy. The actuarial rate of local recurrence in the limb conservation group was 20 per cent at 5 years, and in the amputation group it was zero. The authors comment that this increased local recurrence rate did not result in decreased survival. However, if we take their actuarial overall 5 year survival rate of 88 per cent for the amputation group as representing the survival of patients NOT having a local recurrence, and assume that having a recurrence could reduce the overall 5 year survival of the 20 per cent suffering local recurrence by a factor of two to 44 per cent, then the limb conservation group would be expected to have a survival which was an aggregate of 20 per cent with 44 per cent survival and 80 per cent with 88 per cent survival i.e. an expected 5 year survival rate of 79·2 per cent. It would require 270 patients in each arm of the trial to demonstrate this difference with a significance level of 95 per cent ($\alpha = 1{\cdot}96$) and a power of 80 per cent ($\beta = 0{\cdot}84$)[22]. It is therefore not surprising that the NCI randomized trial did not demonstrate a survival difference, and no conclusions can be drawn from this.

Brennan *et al*[23] have conducted a randomized trial of brachytherapy (interstitial implant irradiation) in 117 patients with localized extremity or trunk sarcomas. Fifty-two patients were randomized to receive brachytherapy and 65 to no brachytherapy. The actuarial probability of local recurrence at 3 years was 5 per cent in the brachytherapy group, and 18 per cent in the no brachytherapy group. The authors comment that this difference in local recurrence rate did not translate into a survival difference. However, if once again we assume that having a local recurrence would decrease the overall survival rate from 88 per cent by a factor of two to 44 per cent (the actuarial survival of the brachytherapy group at last follow-up corresponds closely to the previous NCI figures) then it would require 680 patients in each arm of this trial to demonstrate a survival disadvantage of this magnitude.

Thus, although the comparison of two arms of a randomized trial is statistically the most satisfactory method of determining whether or not local recurrence jeopardizes survival, the practical difficulties of accruing sufficient numbers of patients into even a multicentre trial of local sarcoma therapy will continue to prevent the issue being settled by this means.

Discussion

The different opinions expressed in the literature concerning the influence of local recurrence on survival can largely be accounted for by incautious interpretation of the available data. The most popular methods of examining the outcome of local recurrence are also the most unsatisfactory, as no statistically valid conclusions can be drawn from survival analyses which examine local recurrence as a univariate factor. Multivariate analyses of risk factors for survival are more satisfactory but are limited in their ability to discriminate between multiple interrelated factors unless patient numbers and events are very large, and local recurrence must be recognized as a time-dependent factor. Even if local recurrence emerges as a predictor of survival, a causal relationship cannot be presumed.

The most satisfactory way of addressing the question of local recurrence and survival is to examine prospective randomized trials in which one arm has a high incidence of recurrence. With respect to soft tissue sarcoma, it is unlikely that sufficient numbers of patients will ever be entered into such prospective trials to give a conclusive answer. Even for breast cancer, prospective randomized trials comparing breast conservation therapy with mastectomy may not have the statistical power to demonstrate a survival deficit due to local failure if it is of the order of magnitude of the risk associated with a comparable primary[24].

We may never know for certain whether local recurrence jeopardizes survival. Clinical decisions concerning limb conservation will thus continue to involve an element of value judgement centred on whether the uncertain risks attendant upon conservation are justified by the presumed improvement in quality of life.

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Pathophysiology of ischaemia reperfusion injury: central role of the neutrophil

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Ischaemia is a common clinical event leading to local and remote injury. Evidence indicates that tissue damage is largely caused by activated neutrophils which accumulate when the tissue is reperfused. If the area of ischaemic tissue is large, neutrophils also sequester in the lungs, inducing non-cardiogenic pulmonary oedema. Ischaemia reperfusion injury is initiated by production of reactive oxygen species which initially appear responsible for the generation of chemotactic activity for neutrophils. Later, once adherent to endothelium, neutrophils mediate damage by secretion of additional reactive oxygen species as well as proteolytic enzymes, in particular elastase. Therapeutic options for limiting ischaemia reperfusion injury include inhibition of oxygen radical formation, pharmacological prevention of neutrophil activation and chemotaxis, and also the use of monoclonal antibodies which prevent neutrophil-endothelial adhesion, a prerequisite for injury.

Ischaemia is a common clinical event with potentially serious consequences. Evidence suggests that the major part of tissue injury occurs upon reperfusion and is mediated by activated neutrophils. The ensuing damage, termed ischaemia reperfusion injury, is manifested by oedema and increased microvascular permeability to protein. This resulting injury is thought to be similar in most states of tissue hypoperfusion, including limb ischaemia, transplantation, stroke and hypovolaemic shock. In situations such as myocardial infarction, reperfusion of the occluded coronary artery may not occur and part of the myocardium will inevitably die. Adjacent myocardium will often have its blood supply critically diminished, but will still be viable. It is this poorly perfused area which is subjected to 'reperfusion' injury and the extent of this injury determines eventual infarct size. If the mass of ischaemic tissue is large, such as the legs or the gastrointestinal tract, reperfusion results not only in local damage, but also in lung injury manifest by non-cardiogenic pulmonary oedema – the adult respiratory distress syndrome[1,2]. In this paper we discuss the cellular basis of ischaemia reperfusion injury, review the inflammatory mediators involved and consider potential strategies for treatment.

During the last decade enormous advances have been made in the understanding of the reaction of tissue subjected to ischaemia reperfusion or hypotension. Central to our improved understanding have been two observations. First, reperfusion *per se* causes tissue injury considerably in excess of that induced by ischaemia alone. This was shown dramatically by the fact that the histological changes of injury after 3 h of feline intestinal ischaemia followed by 1 h of reperfusion were far worse than the changes seen after 4 h of ischaemia without reperfusion[3]. Secondly, the neutrophil has been demonstrated to be the prime mediator of the additional injury. It has been known for many years that the neutrophils infiltrate the myocardium after infarction, and their presence was initially thought to be a beneficial part of the healing process[4] However, in 1983 it was observed that the eventual size of a myocardial infarct produced by temporary coronary artery clamping in the dog could be substantially reduced by depleting the animal of circulating neutrophils beforehand[5]. This led to the suggestion that neutrophils actively injure tissue during ischaemia reperfusion and, in fact, largely determine the size of the infarct. Evidence from various experimental models supports this hypothesis, as described below.

More recently, knowledge has rapidly accumulated regarding the mechanism of the neutrophil-mediated injury, including a clearer understanding of the factors responsible for neutrophil recruitment into reperfused tissue, and the means by which neutrophils then cause injury This level of understanding has permitted the development of antagonists with the ability to reduce injury in animal models of ischaemia.

Biochemistry of reperfusion

Reperfusion injury is initiated by biochemical events occurring during ischaemia which result in the generation of reactive oxygen metabolites such as superoxide anion, hypochlorous acid (HOCl) and hydrogen peroxide (H_2O_2)[6]. The first step is the depletion of ATP which is degraded by hypoxanthine. Normally, hypoxanthine is oxidized by the enzyme xanthine dehydrogenase to xanthine using nicotinamide adenine dinucleotide (NAD) in a reaction converting NAD to NADH However, during ischaemia xanthine dehydrogenase, which is usually present in large quantities, is converted to xanthine oxidase. This enzymatic ('D-to-O') conversion is central to the hypothesis of oxygen radical-mediated reperfusion injury Xanthine oxidase has recently been shown to build up during periods of as little as 60 min of skeletal muscle tourniquet ischaemia in humans[7].

The second important event in ischaemia is that excess levels of hypoxanthine accumulate in tissue. This occurs for two reasons: (1) xanthine dehydrogenase is no longer present; and (2) xanthine oxidase uses oxygen as its substrate instead of NAD and is therefore unable to catalyse the conversion of hypoxanthine to xanthine because oxygen is unavailable. Nothing untoward happens as a result of the high levels of xanthine oxidase and hypoxanthine until reperfusion. When oxygen is re-introduced, xanthine oxidase converts hypoxanthine to xanthine with the generation of large amounts of superoxide anion (*Figure 1*). This burst of superoxide production starts a cascade of reactions which release other oxygen radicals and H_2O_2 within endothelial cells[8,9].

Oxygen radicals were shown to be of importance in ischaemia reperfusion injury when injection of superoxide

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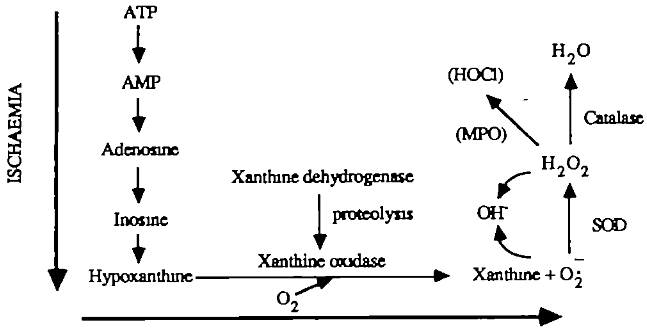

Figure 1 *Ischaemia leads to build-up within endothelial cells of hypoxanthine and xanthine oxidase. The reintroduction of O_2 with reperfusion leads to generation of superoxide anion (O_2^-) and other reactive oxygen metabolites within endothelial cells The hydroxyl radical (OH) may be produced by the reaction of superoxide and H_2O_2 in the presence of Fe^{2+} or Cu^{2+} ions (the Haber–Weiss reaction) or H_2O_2 alone in the presence of Fe^{2+} (the Fenton reaction) Following neutrophil activation, myeloperoxidase (MPO) in the neutrophil generates HOCl SOD, superoxide dismutase (Adapted from Granger[6])*

dismutase, a highly specific scavenger of superoxide anion, prevented the increased capillary permeability occurring upon reperfusion in a feline model of intestinal ischaemia[10]. Others have made similar observations in myocardial ischaemia[11,12]. However, the intracellular onslaught of reactive oxygen species does not by itself appear to be sufficient to account for the extent of injury, because profound protection is afforded in different settings of ischaemia reperfusion injury, either by prior depletion of circulating neutrophils or by preventing their microvascular adherence[5,6,13,14]. In further support of the action of the neutrophil is the observation that treatment before reperfusion with oxygen radical inhibitors or scavengers prevents neutrophil accumulation in reperfused tissue. Initially, we believe that the main pathological effect of oxygen radical release is the generation of chemotactic activity leading to the directed migration of activated neutrophils into the reperfused tissue, with consequent injury[8,13]

Essential role for arachidonic acid products

The precise steps linking xanthine oxidase and reactive oxygen metabolites to chemotactic activity are not well understood. Moreover, the exact nature of the chemotactic agents operative in different settings of ischaemia are unknown, although arachidonic acid products and complement fragments, the latter particularly in myocardial ischaemia, appear to be of key importance[15]. Breakdown products of arachidonic acid are found in high concentrations in plasma soon after reperfusion of ischaemic tissue. One consequence of oxygen radical release is that intracellular free Ca^{2+} rises dramatically, and this is thought to be a crucial step in the activation of plasma membrane phospholipase A_2 and subsequent generation of products of arachidonic acid[16]. Certainly, inhibition of oxygen radicals with scavenging enzymes prevents the release of arachidonic acid metabolites after reperfusion[17], and the superoxide ion seems to be a prerequisite for the generation of neutrophil chemotactic activity[18]. The main pathways of arachidonic acid breakdown are shown in *Figure 2*.

Evidence is lacking that arachidonic acid metabolites induce endothelial injury in ischaemia and reperfusion independently of neutrophils There are, however, three mechanisms by which arachidonic acid products might influence neutrophils in reperfusion injury. First, they could act as chemi-attractants and induce neutrophil adhesion to endothelium. The lipoxygenase product leukotriene B_4 and the cyclooxygenase product thromboxane A_2 are potent chemo-attractants known to do this[19,20]. Evidence suggests that leukotriene B_4 is generated in sufficient quantity in ischaemia reperfusion to induce neutrophil diapedesis[21]. Other observations indicate that lipoxygenase products are of central importance in determining reperfusion injury For example, their inhibition reduces neutrophil accumulation and injury in the myocardium after infarction[22] and following hind limb tourniquet ischaemia[14].

Secondly, arachidonic acid products may activate neutrophils to produce more oxygen radicals and also proteolytic enzymes. Leukotriene B_4 is a potent stimulus for neutrophil generation of hydrogen peroxide and elastase[23], and has been shown to activate neutrophils to induce endothelial permeability *in vitro* and *in vivo*[24]. Thromboxane A_2 also activates neutrophils and mediates their H_2O_2 production following ischaemia[25].

Thirdly, leukotrienes and thromboxane affect blood flow and therefore tissue perfusion by direct action on the microvasculature. For example, thromboxane-mediated vasoconstriction exacerbates poor capillary flow after reperfusion[26] A demonstration of this phenomenon occurs in ischaemia and reperfusion of the kidney where there is debate as to whether reperfusion injury is in fact neutrophil-dependent[27,28] It is thought that the major mechanism of this injury is the development of an imbalance between vasodilating and vasoconstricting agents. The importance of thromboxane is indicated by the ability of vasodilating prostaglandins to attenuate damage, but only if thromboxane is inhibited at the same time[29,30]. The kidney's need for vasodilating prostaglandins is shown clinically by the potential for renal damage following administration of cyclooxygenase inhibitors such as ibuprofen or aspirin, even though these drugs inhibit thromboxane synthesis[31]. The renal injury is due to inhibition of prostaglandin synthesis which limits the ability of the renal vasculature to vasodilate. It is not known whether leukotrienes C_4 and D_4 are important in ischaemia, although they are potent vasoconstrictors[32] Leukotriene B_4 does not directly affect blood flow.

Neutrophil adherence is a prerequisite for endothelial injury

Evidence suggests that neutrophils entering tissue which has just been reperfused become activated to increase synthesis of oxygen metabolites and proteolytic enzymes, and to become more adhesive for endothelium. These neutrophils can then induce injury by adhering to endothelium in two sites the pre-capillary sphincter and the post-capillary venule. As activated neutrophils become more viscous, they may not be malleable enough to pass through the pre-capillary sphincter. The result is that capillaries become plugged (the no-reflow

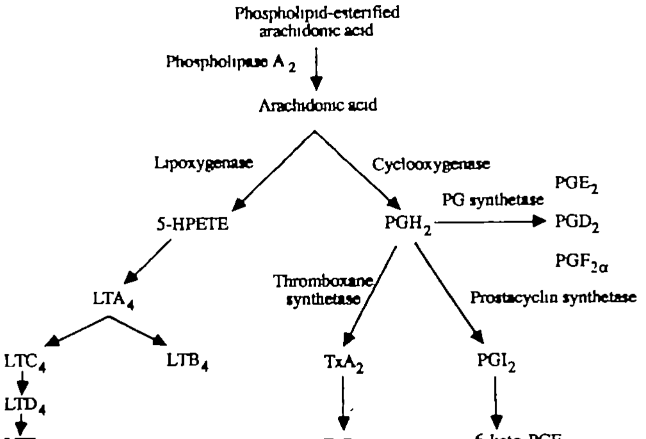

Figure 2 *The arachidonic acid cascade showing essential products and intermediates LT, leukotriene, Tx, thromboxane, PG, prostaglandin*

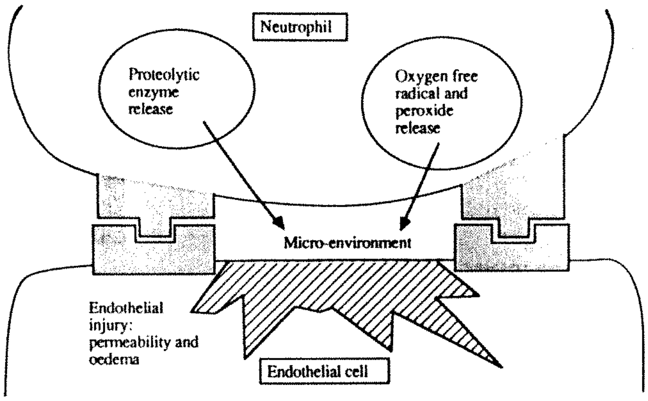
Neutrophil
Proteolytic enzyme release
Oxygen free radical and peroxide release
Micro-environment
Endothelial injury: permeability and oedema
Endothelial cell

Figure 3 *Schematic diagram of neutrophil-mediated endothelial injury. Following binding of its adhesion receptors (the CD 18 complex) to endothelial ligands, the activated neutrophil releases proteolytic enzymes and reactive oxygen metabolites into the extracellular space. This results in increased tissue permeability and oedema*

phenomenon) upon reperfusion, with possible exacerbation of anoxic injury[33]. Most invading neutrophils, however, adhere to endothelium in the post-capillary venule. The mechanism by which neutrophils then induce injury is via the secretion of proteolytic enzymes such as elastase[34], probably in conjunction with neutrophil-generated oxidation products such as HOCl and H_2O_2. These result in lysis of essential structural matrix proteins such as elastin, leading to increased microvascular permeability.

Neutrophils must not only be present but their adherence to endothelium appears to be a prerequisite for microvascular injury (*Figure 3*). Neutrophil-endothelial adhesion is thought to create a microenvironment which permits high concentrations of injurious agents. Initial evidence supporting the importance of adhesion in reperfusion injury was the finding that after intestinal ischaemia, mucosal damage could be prevented by pretreating the animals with a monoclonal antibody directed against the neutrophil adhesive glycoprotein, the so-called CD 18 complex[35]. This antibody inhibited neutrophil accumulation in the reperfused intestinal mucosa by preventing the process of neutrophil adhesion to endothelium. Others have extended these observations of the importance of the CD 18 adhesion molecules to include reduction of injury and neutrophil influx into the heart[36], skeletal muscle[37] and lungs[38] following ischaemia reperfusion of these organs. Furthermore, it has been demonstrated that the endothelial ligand for CD 18, the intercellular adhesion molecule-1 (ICAM-1, CD 54), is also involved in reperfusion injury because an antibody directed against this antigen effectively reduces infarct size, and does so to the same extent as a CD 18 antibody[39]. Moreover, the binding action of neutrophil CD 18 to endothelium appears to be the signal required for the neutrophil to release H_2O_2 and possibly proteases into the extracellular environment[40]. These paired adhesion molecules, CD 18/ICAM-1, are the only antigenic determinants of neutrophil-endothelial adhesion for which clear roles have been demonstrated in ischaemia reperfusion injury.

Treatment with a CD 18 monoclonal antibody also has profound effects in experimental hypovolaemic shock and resuscitation, which might be considered as a form of whole body continuous ischaemia and reperfusion[41,42]. In these studies, not only did treatment with the CD 18 antibody prevent mortality after rabbits were subjected to shock, but it also significantly reduced their requirements for continuing fluid replacement during and after the period of resuscitation. This important finding indicated indirectly that neutrophil activation contributes to the increased microvascular permeability characteristic of shock.

Because microvascular aggregates could exacerbate ischaemia reperfusion injury, and platelets are known to aggregate in response to thromboxane, it has been suggested that these cells might be important in ischaemia reperfusion injury. However, platelets are not thought to be directly involved for several reasons. First, they do not accumulate in ischaemic tissue during reperfusion, as demonstrated by intravital microscopy of skeletal muscle[43] and by using ^{111}In-labelled platelets as a tracer[1]. This contrasts with the consistent presence of neutrophils. Secondly, platelets do not possess CD 18 antigens. Therefore, the protection afforded to reperfused tissue by CD 18 antibodies cannot be explained by an effect on platelets. Thirdly, although stimulated platelets are known to be a prominent source of thromboxane, neutrophils are more likely to be the cells responsible for the generation of thromboxane in ischaemia reperfusion, as prior depletion of circulating neutrophils almost completely inhibits the rise in thromboxane without affecting the platelet count[14]. These considerations do not deny the possible indirect role of platelets whereby their secretion of thromboxane and other agents might trigger neutrophil activation.

Lung injury following lower limb ischaemia

The remote consequence of ischaemia reperfusion is non-cardiogenic pulmonary oedema, an early manifestation of the adult respiratory distress syndrome. This is secondary to neutrophil-mediated abnormal permeability of the lung microvasculature to protein[1,2,44]. It is assumed that the larger the mass of ischaemic tissue, and the longer the ischaemic time, the more probable it is that remote lung injury will occur. Indeed, in a series of 20 consecutive patients undergoing abdominal aortic aneurysm repair, clinical and radiological evidence of pulmonary oedema developed in each case[45]. Experimental models suggest that this injury is also caused by the sequestration of activated neutrophils within the pulmonary microvasculature, because both neutrophil depletion and use of inhibitors of neutrophil activation effectively prevent the resulting pulmonary oedema[46,47]. The mechanism whereby neutrophils selectively accumulate in the lungs to cause injury following ischaemia of the lower limbs is not fully understood. It is likely that additional mediators such as cytokines are involved since in other experimental settings these agents have been found to stimulate neutrophils to adhere to pulmonary endothelium[48]. Cytokines are also involved in the processes determining neutrophil adhesion, by directly activating endothelium to become adhesive for neutrophils[49].

Treatment of ischaemia reperfusion injury

Clearly the avoidance of prolonged periods of ischaemia limits the likelihood of large quantities of hypoxanthine and xanthine oxidase accumulating within ischaemic tissue. However, in clinical situations such as occlusive arterial trauma, transplantation, myocutaneous flaps, and in operations using tourniquets and arterial clamps, the opportunities for ischaemia reperfusion injury are many. How might this injury be limited? Experimental evidence from animal models suggests several possibilities. First, inhibitors of oxygen radicals may be effective in limiting the generation of arachidonic acid products following ischaemia. Indeed we have found that mannitol, which is a hydroxyl radical scavenger, when used at 0·29 g/kg reduced the lung oedema and permeability following aneurysm surgery by a mechanism independent of its ability to promote osmotic diuresis[50]. Allopurinol, a xanthine oxidase inhibitor, has limited ischaemic injury in several animal models as have inhibitors of superoxide dismutase, catalase, iron chelating agents and calcium channel blockers[6]. Secondly, inhibitors of lipoxygenase or thromboxane synthetase might reduce generation of chemo-attractants and thereby prevent neutrophil migration into reperfused tissue, and improve capillary blood flow. Thirdly, a monoclonal antibody directed towards the neutrophil CD 18 complex or endothelial ICAM-1 could be used. The *in vivo* studies reported suggest that antibody therapy

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is an effective means of reducing neutrophil accumulation into reperfused tissue.

Mannitol or other oxygen radical inhibitors may be useful in limiting reperfusion injury in other situations besides aneurysm surgery. These might include operations to release a strangulated hernia or testis, during femoral embolectomy or before revascularization of a traumatically ischaemic limb. Unfortunately, cyclooxygenase inhibitors such as ibuprofen or aspirin are potentially hazardous in these clinical settings because they might hinder renal function through their inhibition of prostaglandins. It remains to be determined whether the other potential treatments mentioned will be of clinical benefit.

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Endothelial cell seeding

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Endothelial cell seeding is a technique that has developed over the past 15 years in response to the need for a high performance synthetic vascular graft. This review details our present knowledge of seeding and examines the various problems that have hampered its introduction into clinical practice.

Small vessel occlusive arterial disease is bypassed most successfully by autogenous vein grafts[1,2]. However, when vein is not available surgeons are obliged to implant synthetic grafts. Factors that are relatively unimportant in large vessel replacement, where synthetic grafts are satisfactory, are highly significant in small vessel bypass. In the latter blood flow is reduced and there is a rapid adsorption and accumulation of blood proteins on to the graft surface[3], with the formation of a thrombogenic pseudointima of compacted fibrin[4]. Because an endothelial cell lining never develops on artificial surfaces in humans[4,5], the pseudointima is retained throughout the life of the prosthesis and may be important in subsequent graft occlusion.

Endothelial cells are actively antithrombotic[6] and provide the best possible local environment for preventing thrombosis. The endothelial lining occupies a pivotal position in the homoeostasis of the vascular tree[7] synthesizing prostacyclin, thromboxane A_2, endothelin and other chemicals that maintain a delicate balance between factors promoting and opposing thrombosis. In addition to haemostasis, endothelial cell physiology contributes to early atherosclerotic change, haematogenous tumour metastasis, transplant rejection and white blood cell emigration to sites of inflammation. Further elucidation of endothelial cell biology may eventually bring therapeutic benefits to patients with widely differing diseases.

The development of an artificial graft lined by active, vascular endothelium (the living prosthesis) would combine the virtues of endothelium with the availability of synthetic materials and could result in a conduit with a performance much nearer to that of autogenous vein. However, seeded artificial grafts may never be as good as autogenous vein, because other important factors such as the chemical nature of prostheses and compliance influence their fate. Despite these limitations, coronary artery bypass grafting, synthetic heart valves, artificial organs and peripheral vascular surgery are all areas that could exploit improvements.

Endothelial cell seeding has developed in response to the need for an improved prosthesis and consists of various techniques to promote the growth of vascular endothelial cells on the luminal surface of artificial grafts. Over a period of 15 years extensive research has culminated in several clinical trials. In this review we discuss the development of endothelial seeding, the problems associated with its implementation, and its possible role in surgical practice.

Isolation and harvesting of endothelial cells

Although techniques to isolate endothelial cells have been available for some time[8], the development of identification procedures and of long-term, *in vitro* culture were important advances[9–11]. Subsequently, endothelial cells were isolated from many different sources[12] but umbilical cord was the first and, because of its availability and convenience, remains the most commonly used source for laboratory work.

There are two principal methods of harvesting large vessel endothelium[12,13], mechanical and enzymatic. Cells can be mechanically harvested by scraping them from the intima, but this may lead to cell damage and contamination with smooth muscle cells. Mechanical harvesting is probably more unreliable and certainly less popular than the enzymatic techniques that have superseded it. These latter techniques bathe the endothelium in collagenase, allowing separation of the cells from the extracellular matrix and basement membrane In the eversion method a vessel is turned inside out and bathed in enzyme[14], whereas in the infusion technique the enzyme is flushed into the vessel. Both are widely used.

Although endothelial cell harvesting is now reported routinely, the success and yield vary with the source Gimbrone *et al.*[15] found that at 12 h after seeding on to tissue culture plastic only 20–50 per cent of harvested cells had attached, and an adequate growth of cells may be possible in only 33–81 per cent of specimens[16–18]. Human long saphenous vein produces a lower yield of viable cells with a longer doubling time compared with cells from animal large vessel endothelium[19]. In addition, non-smokers provide significantly better cell harvests[20].

When large amounts of tissue are available, large numbers of cells can usually be obtained[21]. These cells will grow and migrate most efficiently on tissue culture plastic coated with fibronectin or gelatin[22] and require a culture medium containing glutamine, serum, endothelial cell growth factor and heparin[23–25]. Using these supplements cells may be cultured for long periods.

There have been few attempts to standardize the harvesting of endothelial cells. In one study[26] the average harvesting efficiency was only 12–15 per cent, possibly because even fresh veins have an incomplete endothelial lining Although cell isolation with the infusion technique may be more efficient than with the eversion method[27], in general present harvesting methods are inefficient and yield insufficient cells for confluent coverage of a graft surface[28–30] Twenty-four hours after seeding a graft, as little as 0·27 per cent of the surface may be covered by cells[30]. If this problem is to be overcome an abundant source of endothelial cells is required Although the long saphenous vein is a good source, if sufficient cells are available to line a prosthesis the vein itself is likely to be adequate for arterial bypass. At present no sufficiently abundant source of endothelial cells exists in humans to provide reliable confluent coverage of a prosthetic graft. Current methods of harvesting are relatively inconsistent and empirical and so clinical studies have taken place against a background of poorly defined experimental techniques.

Microvascular endothelial cells and mesothelium

In an effort to overcome the problems associated with procuring large vessel endothelium, researchers have turned to microvascular endothelium, which can be isolated in large quantities

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from omentum[12] and tolerates prolonged culture[31]. Isolation entails enzymatic digestion of the tissue, followed by either separation on a centrifugation gradient[32] or graded meshes[33] Although the cell harvests seem to be lower after centrifugation, equivalent results with both methods are obtained after seeding grafts *in vivo*[34]

The only alternative cell source is the lining of the peritoneal cavity. Peritoneal mesothelial cells are actively antithrombogenic and produce prostacyclin[35]. Preliminary work on their role as vascular graft linings has been undertaken.

A problem that must be faced in the isolation of microvascular endothelium from omentum is contamination with mesothelial cells. Most studies confirm the endothelial origin of their cells by staining for factor VIII-related antigen. However, some workers[36,37] doubt the origin of omentally isolated cells and one study was virtually unable to show any difference between pulmonary microvascular endothelial cells and pericardial mesothelial cells[38]. Recently, monoclonal antibodies against cytokeratins 8 and 18 have been recognized as markers for mesothelial cells. Studies using these markers have suggested that omentally derived cells are mesothelial, not endothelial[39]

Seeding studies

In vitro *studies*

Once the isolation and culturing of endothelial cells became routine, attempts to apply cells to vascular prostheses (seeding) rapidly followed[40]. However, the methods used to isolate and culture cells vary and seeding densities in the laboratory are often at levels presently unachievable in humans. Cells are not always subjected to physiological conditions and the resulting published literature is somewhat confusing and contradictory.

Adhesion on to many artificial surfaces is biphasic[41]. Initial adherence is rapid and virtually complete by 15–30 min. There is then a second phase when adhesion still increases, but at a much slower rate. Although the raw surfaces of Dacron® (E.I. du Pont, Wilmington, Delaware, USA) or polytetrafluoroethylene (PTFE) do not encourage endothelial cells to adhere[42], precoating with a substrate, such as fibronectin or gelatin, improves coverage[43–45] Platelet-rich plasma, amnion-coated Dacron, fibrin glue and combinations of collagens and fibronectin or laminin have also been found to be effective[41,46,47], but with short seeding times seeding efficiencies can be disappointingly low[47]. However, once attached to the graft material, the cells will usually grow successfully[48], especially on PTFE[42].

Once attached to the graft surface the endothelial cells must withstand the shear stresses of circulating blood. Cells are lost rapidly from a seeded graft within the first 30 min, and by 24 h only 4 per cent of the seeded cells may remain[28]. Fibronectin can improve endothelial cell retention in conditions of shear stress[49–51], but this advantage may be offset by its tendency to cause increased platelet deposition on the graft surface[52].

Leucocytes may be partly responsible for endothelial cell detachment. If tissue culture medium is used in an artificial circuit more cells remain attached than when blood is used[43], and endothelial cell retention can be vastly improved in seeded prostheses implanted into leucopenic dogs[53].

Laboratory studies on microvascular endothelial cells are more limited but have shown that initial cell adherence to grafts is rapid and that the cells withstand high shear stresses[54] Plating microvascular endothelial cells on to a pre-established clot at supraconfluent densities (sodding) has produced confluent graft coverage at 3 h[55].

In vivo *studies*

Animals. Seeding synthetic prostheses for *in vivo* use with endothelial cells was first attempted in 1975[40]. Subsequently, seeded grafts have been evaluated using a number of functional assessments. Initially, platelet deposition appears to be greater on seeded grafts than on controls, but by 2 weeks after implantation seeded grafts show less deposition, and platelet survival soon returns to normal, unlike on control grafts in which it remains shortened[56,57] The use of antiplatelet agents in the early postoperative period, combined with seeding, seems to be an especially effective combination[56,58,59]

The thrombus-free surface area is increased and the surface thrombogenicity is reduced in seeded Dacron grafts in dogs and the rapid development of an endothelial monolayer by 4 weeks is associated with thin inner capsules[60–62]. Knitted Dacron is better than woven Dacron at supporting endothelial cell growth[63] and preclotted PTFE grafts also develop good endothelial coverage[64]

The healing of seeded grafts has been closely examined in dogs. The University of Michigan group[14,65] showed that initially both seeded grafts and controls are covered with a platelet carpet and scattered white blood cells. By the fourth day the first signs of endothelialization are present on seeded grafts and from 7 days there is enlargement of the endothelial patches. Seeded grafts are grossly clean and are 60 per cent covered with endothelium by 2 weeks; at 1 month a confluent monolayer with vasa vasorum is present. Similar work[66] confirmed the above findings up to 15 days, but failed to show a significant difference between seeded and unseeded Dacron grafts from 15 days onwards

Improved patency rates have been demonstrated in small-diameter seeded prostheses of Dacron and PTFE, and have been associated with superior platelet survival, clot-free surface area and the development of endothelium[67–71].

Microvascular endothelium from omentum has been used to seed grafts *in vivo*, and produces a rather thick subendothelial layer, although thrombus-free areas are probably equivalent to seeding with large vessel endothelium[72,73]. Seeding with mesothelial cells can also lead to the development of a cellular lining which secretes prostacyclin[74,75].

Some studies[76,77] have been less favourable, especially the endothelial cell seeding of interposition grafts in veins. Two studies have failed to show improved patency using PTFE grafts in dogs[78,79], although in one[79] there was less luminal clot, decreased platelet accumulation, more endothelium and a thinner inner capsule on seeded grafts. The origin of the neointima that forms on the seeded grafts is also the subject of controversy as the process of seeding may create a milieu suitable for host endothelial cell growth[80]. As one would expect, autologous seeding seems to be most effective, supporting seeded cells as the origin of the neointima, but xenograft seeding may also be successful[81]. Placing seeded and unseeded grafts in the same animal, combined with variations in the use of antiplatelet medication, may be possible reasons for these results.

Clinical trials Besides the drawbacks of investigating endothelial cells *in vitro*, many of which also apply *in vivo*, animal studies are compounded by one other crucial problem. Although there are marked differences between species[5,82], all experimental animals develop an endothelial cell lining on a prosthetic graft whether or not it is seeded In contrast, in humans a neointima is probably never formed[4], and there are fundamental differences in the way that animals and humans heal artificial grafts. Despite this, encouraging results from animal work have provoked studies in humans.

Any comparison between seeded and unseeded synthetic femorodistal grafts, in patients with inadequate autogenous vein, presents formidable problems. The small numbers of patients appropriate for this type of surgery, and the large numbers required to construct a trial of sufficient power to establish a difference, would require a multicentre study with facilities for cell harvesting and seeding in each centre. Finally, the time required to confirm the long-term advantages of seeding, if graft occlusion was used as the endpoint, probably precludes such a trial being mounted.

Four centres, at Indianapolis, Dundee, Vienna and Göteborg, have individually undertaken limited trials, using large vessel endothelium for seeding. Because of the many confounding variables and the small numbers of participants in these trials, the overall results are inconclusive. While some have demonstrated that endothelium can develop on seeded grafts in humans[83,84] this is not a consistent finding[85]. Recently endothelium has been positively identified 9 months after implantation of a Dacron mesoatrial graft, seeded with endothelial cells from subcutaneous fat[86]. Clinical trials, though, are hampered by the inability to observe the development of endothelium directly. Instead, platelet deposition and the thrombogenicity index have been used as the primary measurable features.

The first clinical study[87] examined 18 endothelial cell-seeded femoropopliteal knitted Dacron grafts There was no overall difference in patency between seeded and unseeded grafts, although autogenous vein grafts fared better than prosthetic grafts. However, the patency rates of seeded grafts were significantly better in non-smokers. A subsequent report[88] demonstrated an early trend towards improved patency and a reduced uptake of platelets in seeded femoropopliteal PTFE grafts. Unfortunately, these early findings never achieved statistical significance.

The earliest studies used mechanical methods of harvesting cells, and a later trial using enzymatic harvesting of cells and antiplatelet therapy[89], demonstrated cumulative patency rates at 3 months of 93 per cent for seeded and 84 per cent for unseeded femoropopliteal grafts. At 1 year the patency rates were significantly different, with 81 per cent for seeded and 31 per cent for unseeded grafts, and all but one of the seeded graft occlusions occurred in patients with a history of smoking or high carboxyhaemoglobin blood levels. Unfortunately, there were only 17 seeded and 14 unseeded grafts in this trial and similar success has not been repeated.

Zilla *et al.*[90] implanted nine seeded and nine unseeded femoropopliteal and femorocrural 6 mm PTFE grafts coated with fibrin glue. They were unable to find differences in platelet accumulation or platelet survival and relied on platelet factor IV, β-thromboglobulin and shape-changed platelets to indicate advantage in the seeded group[29].

Ortenwall *et al.*[30] used Dacron aortic bifurcation grafts in which one limb was seeded and the other acted as control They demonstrated an early decrease in platelet accumulation on the seeded side and in follow-up studies[91] have shown that platelet deposition on the seeded graft limb has remained reduced, over a period of 12 months Other studies[92] used preclotted femoropopliteal PTFE grafts, seeding either the proximal or distal half of the grafts with endothelial cells In 23 patients the mean thrombogenicity index was significantly reduced in seeded graft segments at 1 and 6 months after implantation, indicating a reduction in platelet deposition. However, five grafts failed to show a response to seeding.

Conclusions

Technical innovations have not produced a prosthetic surface to rival vein and there has been no real progress since the introduction of PTFE around 1976. There is now sufficient expertise with endothelial cells to suggest that further developments in materials might best be directed towards developing flow surfaces conducive to the seeding and growth of endothelial cells.

Given the right surface the best outcome would follow if seeding were to be performed using a large number of cells. Cell isolation and culture techniques need to be improved to facilitate high density seeding. Genetic manipulation of endothelial cells[93] and cryopreservation of cells[94] may be important in the future

The development of an off-the-shelf graft, prelined with cells, would combine an active antithrombogenic lining at the time of implantation with a possible reduction in infection[95,96]. This would eliminate the time required for vein harvesting in peripheral vascular surgery, and the availability of such a graft would encourage distal bypass. However, until techniques improve, the adoption of seeding into routine surgical practice cannot be supported outside clinical trials.

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Results of the Duhamel operation in the treatment of idiopathic megarectum and megacolon

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The results of the Duhamel operation in patients with idiopathic megarectum and megacolon have been reviewed. Twenty patients (14 males, six females) underwent the Duhamel operation over a 17-year period for this condition. The mean age at operation was 25 years, the mean age of onset of constipation was 3 years; and the mean follow-up period was 4·5 years. All the resected colons were of enlarged diameter. There was agreement between the preoperative radiographs and the operative specimens with regard to which parts of the rectum and colon were dilated. Subjective feelings of well-being were generally improved by surgery, as was bowel frequency in ten patients. Soiling, straining, abdominal pain and distension were, however, common after operation. Early complications were also common and five patients required further surgery for constipation. The Duhamel operation for megarectum and megacolon is characterized by an improved sense of well-being and improved bowel frequency, but it is associated with the persistence of many symptoms and further surgery is often required.

Patients with idiopathic megarectum, with or without megacolon, form a distinctive clinical group. They may have the onset of symptoms in childhood or in adulthood[1]. Abdominal pain, infrequent defaecation, soiling and recurrent faecal impaction are the major symptoms. Many patients can be managed with regular laxatives, but in a few surgery is required owing to failure of medical treatment or an inability to comply with the therapy, and subsequent persistence of symptoms.

The Duhamel operation was originally described in 1956 for the treatment of Hirschsprung's disease[2] and has subsequently been applied to the treatment of idiopathic megarectum and megacolon. Very few studies have detailed the results of this operation for this condition[3]. This paper examines the results of the Duhamel operation for idiopathic megarectum, with or without megacolon, in one hospital over a 17-year period (1972–89).

Patients and methods

Twenty patients underwent the Duhamel operation for idiopathic megarectum and megacolon between January 1972 and December 1989. All have been included in the study. The case records were reviewed for all patients and in addition it was possible for 17 of these patients to be interviewed by one investigator (G.S.). Information after operation was not available for one patient but his preoperative data are included in this report. Hirschsprung's disease was ruled out by the presence of the rectosphincteric reflux or a full-thickness rectal biopsy, or both.

Patients have been divided according to age at onset: childhood onset (0–10 years) and adult onset (10 years onwards), according to previously stated criteria[1]. Idiopathic megarectum was radiologically defined as a rectal diameter of >6·5 cm in the lateral view at the pelvic brim[4]. Patients were also divided, depending on the radiological findings, into those with a megarectum only and those with a megarectum and megacolon, to ascertain how outcome was related to these different conditions. Preoperative radiographic findings were correlated with the dimensions of the operative specimens.

Constipation was defined as a bowel frequency of less than two movements per week[5]. Patients were interviewed about the presence or absence of symptoms before the operation and at the time of interview. They were also asked to classify their well-being before and after operation as very poor, poor, well, or very well.

There were 14 male and six female patients. The mean age at operation was 25 years (range 12–68 years). The mean age of onset of symptoms was 3 years (range 0–16 years). The mean follow-up period was 4·5 years (range from 6 months to 17 years). Nineteen patients had a childhood onset and one had an adult onset.

Previous medical conditions included one patient with gastro-oesophageal reflux and two with urinary retention. Two patients had previously suffered from depression, one patient was epileptic, and another had Down's syndrome.

Eight patients had previous bowel surgery: left hemicolectomy (one case), transverse colostomy (one case), appendicectomy (one case), anal sphincterotomy (one case), subtotal colectomy with ileorectal anastomosis (one case), two previous exploratory laparotomies plus a previous transverse colostomy and a resection of upper rectum and sigmoid colon (one case), resection of upper rectum and sigmoid colon (two cases). Nine patients had previous manual disimpactions.

All patients had a barium enema before operation, which showed a dilatation of the rectum and left colon in 18 and a dilatation of the whole colon in two patients. The rectum was larger than normal in all patients, i.e. >6·5 cm in diameter in a lateral view of the pelvic brim on a radiograph. The rectal diameter ranged from 10 to 14 cm on radiograph, with a median diameter of 12 cm. The bowel was found to be dilated at the time of operation in all patients.

Bowel frequency, often with the use of laxatives, before and after operation is shown in *Table 1*. One patient had a normal bowel frequency before operation but he had to strain excessively and evacuation was painful.

All patients had a modified Duhamel procedure[6] carried out. The dilated upper rectum and colon were mobilized for resection. The retrorectal space was entered in the midline and a tunnel was made down to the puborectalis. The upper rectum and dilated colon was resected and the open end of the retained rectum, 8–10 cm in length, was closed.

A transverse incision through the posterior wall of the upper anal canal just below the upper border of the puborectalis was made using a peranal approach. The mobilized left colon was then brought down retrorectally through the postanal incision and an end-to-side anastomosis was constructed. The anastomosis was then enlarged by removing a wedge-shaped segment of rectal and colonic wall from above the anastomosis, either by the appliance of clamps or more recently with GIA® (US Surgical Corporation and Auto Suture UK, Ascot, UK) staplers. Most operations were performed by one surgeon (P.R.H.).

Results

All the resected colons were of enlarged diameter. Four had some bowel wall hypertrophy and three had melanosis coli: otherwise they were macroscopically unremarkable. The nerve

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Table 1 *Symptoms before and after operation*

	Before operation ($n=20$)	After operation ($n=19$)
Bowel frequency		
<2 per week	19 (95)	7 (37)
Between 3 per day and 3 per week	1 (5)	10 (53)
>3 per day	0	2 (11)
Laxative use	19 (95)	8 (42)
Straining	9 (45)	7 (37)
Faecal impaction	13 (65)	5 (26)
Painful evacuation	6 (30)	2 (11)
Digital evacuation	1 (5)	1 (5)
Abdominal pain	13 (65)	9 (47)
Abdominal mass	11 (55)	4 (21)
Abdominal distension	14 (70)	11 (58)
Incontinence		
Flatus	12 (60)	8 (42)
Liquid	12 (60)	8 (42)
Solid	6 (30)	0
Soiling	12 (60)	8 (42)
Subjective well-being.		
Very well	0	2 (11)
Well	0	11 (58)
Poor	15 (75)	5 (26)
Very poor	5 (25)	1 (5)

Values in parentheses are percentages

plexuses and ganglia appeared normal in all specimens using haematoxylin and eosin staining. For all patients there was agreement between the radiographic findings before operation and the operative finding regarding which parts of the rectum and colon were dilated.

No patient had excessive bleeding, damage to local structures such as the seminal vesicles or nervi erigentes, or urinary or sexual complications from the operation. Surgery succeeded in increasing bowel frequency in many patients; ten had a normal frequency (from three per day to three per week), but two had diarrhoea and seven were still constipated. Soiling and incontinence of flatus and liquid stool were still present in eight patients and laxatives were used by eight (*Table 1*).

Complications were common in the early period after operation. Three patients had a pelvic abscess, all of whom required an examination under anaesthetic and drainage. However, they had a good outcome, with eventual normal bowel frequency. Five patients had a faecal fistula, four of which settled spontaneously; three of these patients now have a normal bowel frequency and one was lost to follow-up. One patient who had a faecal fistula required a temporary transverse colostomy; after closure he was still constipated. One patient had a rectovaginal fistula which required a repair and a temporary covering colostomy; this patient also remained constipated after colostomy closure.

Late complications included bowel obstruction in four patients. In three of these patients adhesions were divided; in the fourth adhesions were divided and an abscess was drained.

Further surgery for constipation was performed in five patients; two had a puborectalis division, one a right hemicolectomy and later an ileostomy, one a coloanal anastomosis, and the fifth patient had an end colostomy.

Of the two patients with a radiologically defined megacolon, both had a normal bowel frequency after operation although one had soiling and abdominal distension.

Discussion

These results demonstrate that most patients undergoing a Duhamel procedure for megarectum or megacolon feel improved by the operation and have their bowel frequency enhanced. However, there is a considerable number of early complications after operation. Many patients also require further surgery, either because of adhesions and bowel obstruction or because of persistent constipation. Many continue to soil and experience abdominal pain and distension, although these features are often improved.

These results differ from those found when the operation is performed for Hirschsprung's disease[7]. In a series of 39 patients having a Duhamel operation for Hirschsprung's disease, there were three postoperative abscesses and two fistulae. Thirty-six patients were considered to have excellent results. In the only other major description of the Duhamel operation for megarectum and megacolon, Parc *et al.*[3] reported good results in most of their 34 patients, with constipation in only two. Two patients had a pelvic abscess requiring a temporary colostomy and another had a postoperative obstruction treated conservatively. However, five patients had a late anastomotic stricture

The cause of megacolon and megarectum is unknown. In particular, we do not know whether the rectal abnormality is primary or secondary to a sphincter disturbance. The fact that some patients fare well after the Duhamel procedure, despite a probably abnormal rectum remaining partly *in situ*, may relate to the presentation of liquid stool to the rectum.

Alternative operations for this condition include colectomy and ileorectal anastomosis or caecorectal anastomosis[8–10], Swenson-type pull-through[10], coloanal anastomosis[11], and anal myectomy[12]. Our published experience with colectomy consists of a series of 14 cases[8] in which five patients had a colectomy and a caecorectal anastomosis, three had a colectomy and an ileorectal anastomosis, three had a sigmoid colectomy, two had a left hemicolectomy and one had a colectomy with an ileosigmoid anastomosis. Colectomy had a satisfactory outcome. Our recent data showed that colectomy had a good functional outcome with few complications; however, the comparison is limited in that those patients who had a Duhamel procedure had, on average, a greater rectal diameter than those having a colectomy[13]. A recently described alternative operation for this condition is a restorative proctocolectomy with ileoanal anastomosis[14]; five patients who had this procedure for megarectum and megacolon were no longer constipated after operation.

The difficulty in choosing the best operation for this condition resides in its heterogeneous nature, the difference between juvenile and adult onset disease, and the variety of operations that are available. This is compounded by the lack of understanding of the abnormality present.

Given the mixed results of this operation for idiopathic megarectum and megacolon, we would make the following recommendations. In those patients with a moderately dilated rectum or dilated colon who are unresponsive to all medical therapy, we consider that a colectomy with an ileorectal anastomosis[13] offers the best results. In those patients with a grossly dilated rectum and distal colon, the Duhamel operation must be considered, because it involves excision of most of the dilated segment. However, the results are not as uniformly satisfactory in this group of patients.

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Intraoperative localization of colorectal cancers using radiolabelled monoclonal antibodies

Radiation detectors may allow the intraoperative localization of small cancer deposits following administration of radiolabelled tumour-associated antibodies. This technique was evaluated in 16 patients with colorectal tumours (14 cancers, one adenoma, one lipoma) with the ^{111}In-labelled monoclonal antibody (MAb) ICR2 which recognizes the tumour-associated epithelial membrane antigen (EMA). At operation counting was carried out (3 × 20 s per site) using a hand-held radiation probe over the primary lesions and any palpable lymph nodes in the mesocolon. The tumour to normal colon (T/NC) ratio of counts recorded at operation was more than 1·5:1 in eight of the 14 patients with cancer (mean(s.d.), 1·54(0·41):1) and 0·91:1 and 1·06:1 respectively in the two patients with benign tumours. Node to normal colon ratios were higher in lymph nodes containing metastases. The uptake of radiolabelled antibody (T/NC ratio) was higher in EMA-expressing cancers than in those not expressing the target antigen (mean(s.d.), 2·45(0·65):1 versus *1·40(0·20):1,* P *= 0·019). An abdominal tumour model was also developed. Radioactively filled containers of 0·5–10 ml representing tumour deposits were suspended in a tank of ^{111}In solution representing the background activity found in normal tissues. The ratio of radioactivity in the 'tumour' to that of background varied from 2:1 to 8:1. The 'tumour' was considered to be detectable if the mean counts recorded over the 'tumour' exceeded the mean of counts recorded over background by three standard deviations. At a ratio of 2:1 only 'tumours' greater than 5 ml could be detected with a sodium iodide probe and those over 10 ml could be detected with a cadmium telluride (CdTe) probe. At a ratio of 8:1, 'tumours' of 0·5 ml could be detected with either probe. At all ratios and counting periods the NaI probe was more sensitive than the CdTe.*

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Of patients presenting with colorectal cancer less than half will survive 5 years, resulting in over 18 000 deaths annually from this disease in the UK[1,2]. Surgical treatment fails in those undergoing potentially curative resection due to an inability to detect and eradicate local or metastatic tumour at the time of the primary resection. Serial computed tomographic scans and both intraoperative and endoluminal ultrasonography offer significant improvement in staging and in the detection of recurrent colorectal cancer[3–6]. Difficulties arise with these procedures in differentiating tumour from non-tumour tissue[7,8] and hence interest has turned to the use of radiolabelled tumour-associated monoclonal antibodies as physiological imaging agents.

Radioimmunoscintigraphy, however, is rarely able to detect tumour deposits less than 2 cm in diameter[9,10] By using an intraoperative γ-detecting probe following administration of radiolabelled monoclonal antibodies, smaller lesions may be detected than by external imaging with a γ-camera due to the shorter distance between source and detector and a reduction in the proportion of scattered activity detected. This technique was first described in 1984 by Aitken *et al.* in a clinical study and in an animal xenograft model[11]. Subsequent animal and human studies, mostly using the monoclonal antibody B72·3 which recognizes the Tag 72 antigen, have confirmed the value of this technique for localizing tumour deposits at operation and some tumour deposits have been localized which would not have otherwise been detected[12–18].

In the present study a monoclonal antibody has been used which recognizes an epithelial membrane antigen (EMA) expressed by over 80 per cent of colorectal cancers. On immunohistochemical studies this antibody shows greater specificity for colorectal cancer than anticarcinoembryonic antigen[19–21]. The monoclonal antibody, ICR2, has been labelled with the γ-emitting radionuclide ^{111}In whose energy of emissions (171 and 247 keV) and half-life (2·8 days) make it suitable for antibody labelling. This preparation, ^{111}In-ICR2, has been evaluated clinically for the intraoperative detection of tumour deposits in patients with primary colorectal tumours. As a consequence of this study an experimental model was established to evaluate the potential and limitation of the technique, in particular the minimum size of tumours detectable with variation in the radiation detector employed and the tumour uptake of radioactivity.

Patients, materials and methods

Clinical study

Patients Sixteen patients were studied (six men and ten women) with a median age of 69 years (range 51–83 years) In 14 of these

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Table 1 *Clinical details of the patients*

Patient no.	Age (years)	Sex	Diagnosis	Site	Dukes' classification	Differentiation
1	60	M	Adenocarcinoma	Rectosigmoid	B	Moderate
2	83	F	Adenocarcinoma	Rectosigmoid	B	Moderate
3	51	M	Adenocarcinoma	Hepatic flexure	B	Moderate
4	71	M	Adenocarcinoma	Rectum	C*	Moderate
5	79	F	Adenocarcinoma	Transverse colon	B	Moderate
6	58	F	Adenocarcinoma	Rectum	B	Moderate
7	67	F	Adenocarcinoma	Sigmoid	C	Moderate
8	54	F	Adenocarcinoma	Sigmoid	C	Moderate
9	74	F	Adenocarcinoma	Sigmoid	B	Moderate
10	76	F	Adenocarcinoma	Sigmoid	B	Moderate
11	64	M	Lipoma	Sigmoid	–	–
12	76	F	Adenocarcinoma	Splenic flexure	B	Moderate
13	73	F	Adenoma	Caecum	–	–
14	73	F	Adenocarcinoma	Sigmoid	C	Well
15	67	M	Adenocarcinoma	Rectosigmoid	C*	Moderate
16	56	M	Adenocarcinoma	Sigmoid	B	Moderate

* With liver metastases

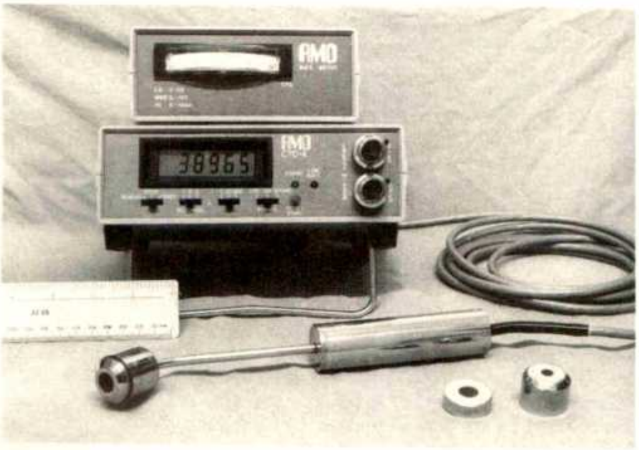

Figure 1 *The cadmium telluride probe, counting unit and ratemeter consisting of a cadmium telluride detector connected to a counting unit which may be set to count over a fixed time period. The ratemeter provides both a visual and audible indication of the number of counts being detected*

patients the histology of the resected specimen showed colonic adenocarcinoma (nine Dukes' B and five Dukes' C, two of whom had liver metastases) and in two patients benign tumours were found (one lipoma of the sigmoid colon and one tubulovillous adenoma of the caecum) (*Table 1*).

Monoclonal antibody. The monoclonal antibody ICR2 is an IgG_{2a} antibody which has been raised in the rat by hybridoma technology using extracts of human milk fat globule membrane at the Institute of Cancer Research, Sutton, UK. This antibody recognizes the EMA antigen which is expressed by the majority of adenocarcinomas but especially those of the breast, ovary and colon[19]. Before patient use the antibody preparation was screened for the presence of bacteria, viruses and endotoxins (Safepharm, Derby, UK).

Antibody labelling and administration. To facilitate radiolabelling with ^{111}In, the monoclonal antibody was first conjugated to the metal chelating agent diethylene triamine pentacetic acid via the bicyclic anhydride (ccDTPA) at a 2:1 molar ratio. Any free DTPA was separated by dialysis (Medicell, UK) against Hepes buffer (pH 7·5) and by gel chromatography on Sephadex G25 (Pharmacia, Upsalla, Sweden). The ICR2–DTPA conjugate was then labelled with ^{111}In by the method of Carrasquillo *et al.*[22] and any unbound ^{111}In was separated by gel chromatography (Sephadex G25). Radiochemical purity was assessed by thin layer silica gel chromatography. One milligram of antibody was labelled with 100 MBq (2·7 mCi) ^{111}In and was administered intravenously over 15 min having excluded hypersensitivity by skin testing. Following administration, temperature, pulse and blood pressure were monitored half-hourly for 6 h.

Intraoperative probing. Intraoperative probing was carried out at 3–6 days after ^{111}In-ICR2 administration using a cadmium telluride (CdTe) semiconductor probe designed for the intraoperative detection of ^{111}In (Radiation Monitoring Devices, Watertown, Massachusetts, USA) (*Figure 1*). At the start of the operation and before mobilization of the tumour a minimum of three 20 s counts were recorded with the probe held over three regions of the primary lesion, two sites over normal colon, any lymph nodes palpable within the mesocolon and over both the right and left lobes of the liver.

On completion of probing the operation was carried out as planned. The resected specimen was then probed at the same sites counted intraoperatively and for the same period to determine the influence of normal tissue background activity on intraoperative measurements. Biopsies of tumour, taken from the growing edge of an ulcerated lesion (or a representative area if polypoidal), and of normal colon were then weighed and counted in a γ-well counter allowing the radiolabelled antibody uptake to be calculated per gram of tissue. Tumour to normal colon (T/NC) ratios for counts obtained at intraoperative and resected specimen probing and the γ-well counting of tissue specimens were calculated.

Tumour antigen expression and the uptake of radiolabelled antibodies. Sections of the resected tumours were stained immunohistochemically using the indirect immunoperoxidase staining method to assess expression of EMA which was graded 0 or 1–4 by the percentage of antigen positive cells[23]. This system of immunohistochemical grading has been shown previously to be reproducible[24].

Statistical methods in the clinical study. Results were compared between groups using Student's *t* test, Spearman rank correlation coefficients and Bland and Altman analysis.

Experimental evaluation

To investigate further the potential and limitations of intraoperative radioimmunolocalization a model was designed in which a radioactive tumour lay within a radioactive background, the levels of radioactivity in both corresponding to those found in patient studies. This system has been used to evaluate two currently available intraoperative probes. By investigating a range of tumour volumes and ratios of radioactivity between tumour and background, the minimum tumour size detectable with each of the probes could then be established for a given range of tumour to normal tissue ratios and counting times.

Table 2 *Results of the clinical study*

Patient no.	Diagnosis	Site	T/NC count ratios		
			Operation	Resected specimen	Well count
1	Carcinoma	Rectosigmoid	1·66	4·50	3·2
2	Carcinoma	Rectosigmoid	1·98	5·13	3·4
3	Carcinoma	Hepatic flexure	N/A	1·23	1·8
4	Carcinoma	Rectum	1·64	4·00	2·0
5	Carcinoma	Transverse colon	1·81	2·73	1·2
6	Carcinoma	Rectum	1·66	4·45	2·1
7	Carcinoma	Sigmoid	2·13	5·87	N/A
8	Carcinoma	Sigmoid	1·20	6·82	3·5
9	Carcinoma	Sigmoid	0·90	4·22	1·6
10	Carcinoma	Sigmoid	1·00	6·25	2·3
11	Lipoma	Sigmoid	0·91	3·40	1·6
12	Carcinoma	Splenic flexure	1·32	4·90	2·3
13	Adenoma	Caecum	1·06	2·70	1·4
14	Carcinoma	Sigmoid	2·06	3·35	1·9
15	Carcinoma	Rectosigmoid	1·57	5·15	3·0
16	Carcinoma	Sigmoid	1·07	5·69	2·3

T/NC count ratios, mean counts on tumour to that of normal colon; N/A, not available

Biodistribution data. The model was based on data available from studies on patients with cancer in whom ^{111}In-labelled monoclonal antibodies had been administered. The percentage of the injected dose of radioactivity taken up by tumour tissue was obtained from the few studies which have provided these data (including the present study) and was taken as 0·001 per cent of the injected dose per gram[25,26]. The injected dose of radioactivity of 100 MBq of ^{111}In is an approved dose for patient administration commonly use for localization studies. Tumour to background uptake ratios of from 2:1 to 8:1 were studied, covering the range reported in clinical studies[27–30]. The background activity was calculated from biodistribution data obtained in the present clinical study based on the injected activity, uptake in tumour tissue per gram and the T/NC ratio and tumour to blood ratio found in biopsy specimens[26].

The model of the intra-abdominal tumour. Hollow containers of 0·5–10 ml were used to represent the tumour deposits. The smaller sizes were constructed from test tubes in which the liquid was sealed using dental moulding wax and the larger sizes were formed from latex rubber. These contained a solution of ^{111}In, with the concentration of radioactivity being altered for each tumour to background ratio examined.

A tank (30 × 28 × 20 cm) was used to represent the abdominal cavity. This was filled to a depth of 17 cm with a solution of ^{111}In at a concentration of 0·5 kBq/ml to give a volume of 15 litres. Sufficient concentrated HCl was then added to give a final tank pH of less than 2, this being required to prevent aggregation of the ^{111}In due to the formation of $^{111}\mathrm{In(OH)}_n$. The level of radioactivity present in the tank was checked before commencing each probe study by removing an aliquot and counting it in a γ-well counter. The count was compared with the counts obtained from an aliquot of the solution used in the preparation of the tumours to ensure that the tumour to background count ratio was kept within 5 per cent of that required.

γ-detecting probes. Two types of radiation detector were evaluated. The first comprised a sodium iodide (NaI) scintillation detector with a crystal 20 mm thick and 26 mm in diameter connected to a photomultiplier tube, power supply and pulse processing and display modules. The collimation, the lead shielding around the aperture in front of the crystal which dictates the window viewed by the crystal, was designed in house for the intraoperative detection of ^{111}In. This detector system was compared with a commercially available CdTe semiconductor probe used in the clinical study which again had been customized for use wth ^{111}In and which was supplied with both wide angle (w.a.) and parallel hole (p.h.) collimators (*Figure 1*).

Tumour positioning. The 'tumours' were positioned in the centre of the tank representing background activity, the upper surface being held 1 cm below the fluid surface. The probe examined was positioned over the 'tumour' with the collimator face parallel to and touching the active background. An energy window for counting of 120–300 keV was chosen for both probes to allow the two γ-emissions of ^{111}In (171 and 247 keV) to be counted.

Counting and statistical analysis. For all 'tumour' sizes and all uptake ratios, counting with both probes was carried out for both 20 and 100 s and repeated three times. The 'tumour' count was obtained by counting directly over and 1 cm above the 'tumour' and the background count was taken at a site remote from the 'tumour', which was chosen to be 10 cm laterally. The shorter counting interval was selected as a practical time period for counting over one site at operation. Because the technique of tumour detection by intraoperative probing of radiolabelled monoclonal antibodies is based on detecting a difference between tumour and background counts of radioactivity, a longer counting period was also investigated to allow the importance of higher counts and hence improved counting statistics to be analysed. The statistical significance of the difference in counts was assessed by calculating the number of standard deviations of the difference between the mean count obtained over the tumour and that over background (decay corrected) using Poisson statistics[26,31,32]. Three standard deviations of the difference between the mean tumour and background counts was taken as a significant level of detectability as this has less than a 1 per cent chance of being due to random counting errors.

Results

Clinical study (Table 2)

The T/NC ratio of counts was greater than 1·5:1 in eight of the 14 patients with cancer (mean(s.d.), 1·54(0·41):1). The two benign tumours showed no selective uptake with ratios of 0·91:1 and 1·06:1 respectively. The correlation between the counting ratio found at operation and those found on γ-well counting of biopsies, taken as the absolute uptake of ^{111}In-ICR2, was poor (Spearman rank correlation coefficient $n=14$, $r=0·19$, $P=0·52$) (*Figure 2*). Probing over the resected specimen resulted in higher T/NC ratios than those found at operation (mean(s.d.), 4·61(1·25):1 *versus* 1·46(0·43):1, $P<0·001$) or on γ-well counting of biopsies (4·30(1·47):1 *versus* 2·24(0·73):1, $P<0·001$) and a good correlation was found between the counts obtained on probing the resected specimen and on γ-well counting of biopsies (Spearman rank correlation coefficient $n=15$, $r=0·84$, $P<0·001$) (*Figure 3*). The Bland and Altman plots (*Figures 4* and *5*) demonstrate that intraoperative probing had a tendency to read a lower value for the T/NC ratio than that found on γ-well counting of biopsies with a mean bias of

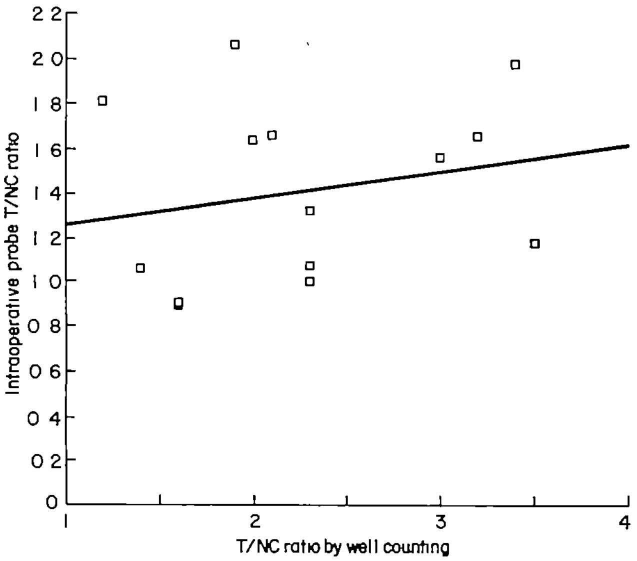

Figure 2 *Correlation between intraoperative probing and well counting The correlation is shown between the ratio of counts obtained by probing over the tumour and over normal colon at operation (T/NC ratio) against the T/NC ratio obtained by counting tumour and normal colon biopsies from the resected specimen in a γ-well counter*

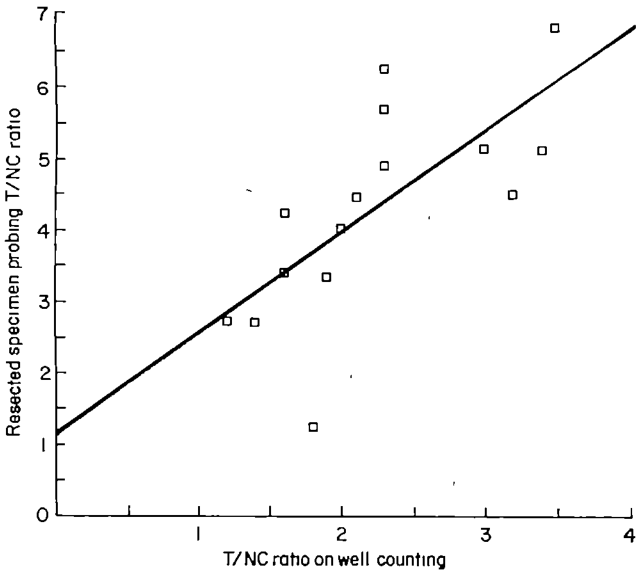

Figure 3 *Correlation between resected specimen probing and well counting The correlation is shown between the mean tumour to normal colon (T/NC) ratio of counts found on probing the resected specimens and those found on counting biopsies of tumour and normal colon from the resected specimen in a γ-well counter*

—44 per cent (95 per cent normal range —116·8 to 28·9 per cent). In contrast, probing the resected specimens gave a higher count than the γ-well counting of biopsies with a mean positive bias of 60 per cent (95 per cent normal range —3·4 to 123·4 per cent). The discrepancy between the specimen probing and γ-well counting T/NC ratios appears to increase with higher uptake ratios.

Ten of the 16 patients had intraoperative probing of lymph nodes palpable in the mesentery of the bowel involved with the cancer. These were all enlarged but less than 1 cm in diameter and none was macroscopically involved with tumour. Three of these ten lymph nodes were subsequently shown on histological examination of the specimen to contain metastases The node to normal colon ratio of counts for those containing tumour was higher in all cases than for those which did not (*Figure 6*).

Probing over the liver gave high count rates with normal liver showing higher counts than the primary cancers (mean(s.d), 2·47(1·10):1) and no liver metastases were localized (present in two patients).

The specificity of uptake of ^{111}In-ICR2 in colorectal cancers was demonstrated by comparing the antigen expression of the resected tumours with the T/NC ratios found on γ-well counting of tumour and normal colon (*Table 3*). Antigen-expressing tumours had significantly higher T/NC uptake ratios than those which did not express the target antigen or which showed focal staining alone (mean(s.d.), 2·45(0·65).1 *versus* 1·40(0·20):1, $P=0{\cdot}019$).

Experimental evaluation

An example of the results of the statistical analysis is shown in *Table 4* (CdTe probe, 100 s counting period and parallel hole collimator). The mean counts for both 'tumour' and background have been calculated for each 'tumour' size at each

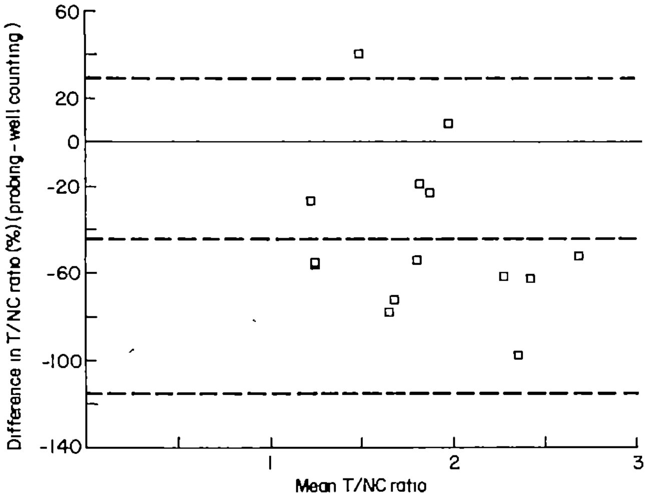

Figure 4 *Bland and Altman plot of tumour to normal colon ratios (T/NC ratio) relating the discrepancy between intraoperative probing and well counting of biopsies. The dashed lines indicate the mean bias and the 95 per cent normal range for the discrepancy between the two counts*

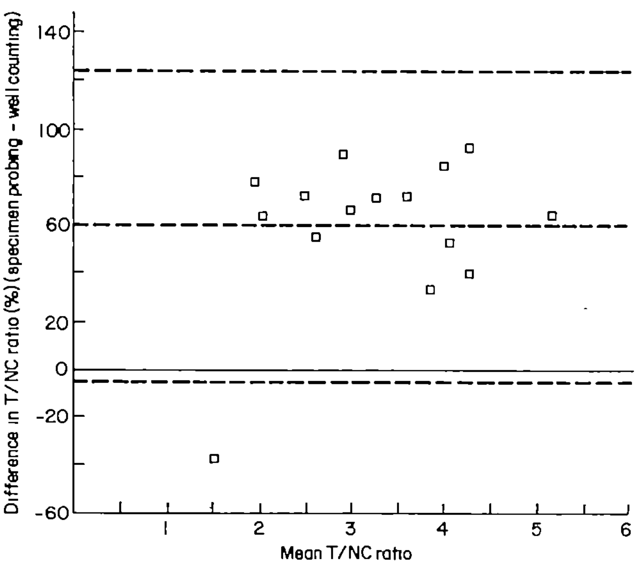

Figure 5 *Bland and Altman plot of tumour to normal colon ratios (T/NC ratio) relating the discrepancy between probing the resected specimen and the γ-well counting of biopsies. The dashed lines indicate the mean bias and the 95 per cent normal range for the discrepancy between the two counts*

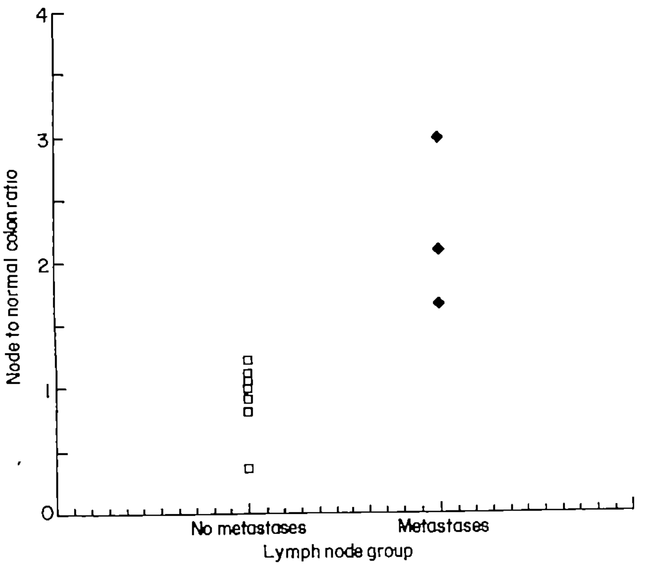

Figure 6 *The mean node to normal colon ratios for the ten patients in whom probing was carried out over enlarged mesenteric lymph nodes. The nodes have been separated into those containing metastases on histological examination (◆) and those which did not (□)*

Table 3 *Antigen expression of the tumours and their uptake of radioactivity (T/NC ratio)*

Grading of antigen expression				
Negative or focal	I	II	III	IV
1·2	2 3	3 2	3 4	
1·4	3 5	1·8	2·1	
1 6		2 0	1 9	
		2 3	3·0	
		1·6		
		2 3		

'tumour' to background ratio and the number of standard deviations of the difference in counts calculated. For both probes and both counting periods a trend was noted for the difference in counts between 'tumour' and background to increase with increase in 'tumour' size and 'tumour' to background ratio. By defining three standard deviations between the mean counts over the 'tumour' to that over normal colon as a threshold of detectability with a 2:1 'tumour' to background ratio and a 20 s count period, none of the 'tumours' was detectable with the CdTe probe whereas only the 10 ml 'tumour' was detectable with the NaI probe. With a counting period of 100 s at this ratio the 10 ml 'tumour' could be detected with the CdTe probe (p.h.) and those of 5 and 10 ml with the NaI probe. At an 8:1 'tumour' to background ratio both probes could detect 'tumours' of 1 ml and above when counting for 20 s, and detected all 'tumours' with a 100 s count. A summary of the 'tumour' sizes detectable, based on the use of three standard deviations as a threshold of detectability, is shown for the different probes, uptake ratios and counting times in *Table 5*.

Discussion

In this clinical study 85 per cent of the patients with colorectal cancer had elevated counts over the primary cancer at operation compared with that of normal colon and the T/NC ratio was greater than 1·5:1 in 57 per cent of patients. In a similar study carried out by Sickle-Santanello and colleagues[14] intraoperative probing resulted in a T/NC ratio of greater than 1·5:1 in 83 per cent of patients with colorectal cancer studied using the ^{125}I-labelled MAb B72·3 This similarity in results may be explained by the target antigen Tag 72 having a tissue distribution similar to that recognized by the MAb ICR2[19,33,34] and the possibility therefore arises that these antibodies may be recognizing different epitopes of the same antigen.

The poor correlation between the *in vivo* T/NC ratios found at operation and that on γ-well counting of biopsies is largely due to the background uptake of radiolabelled antibody, as demonstrated by the higher T/NC ratios found on probing the resected specimens. The latter was also shown to correlate better with the well counting of tissue biopsies. The Bland and Altman plots have clearly shown that the intraoperative probing produces a negative bias in the T/NC ratio obtained when compared with that calculated by γ-well counting of biopsies whereas a significant positive bias is produced by probing the resected specimens. The bias found when probing is compared with γ-well counting of biopsies is likely to be due to background activity in the first case and the mass of the tumour in the latter. The uptake of activity in non-tumour tissue which produces background radioactivity occurs with all antibodies due to the presence of cross-reacting antigens and the removal of antibody by the reticuloendothelial system, but is a particular problem with the liver and spleen when labelling with ^{111}In[27,35,36]. The reason and mechanism for this uptake has not, however, been established[37].

As in previous studies, the results from carrying out intraoperative probing with radiolabelled MAbs did not influence the management of patients with primary colorectal cancers[12–14]. The results do, however, suggest the likely value of this technique in patients with suspected recurrences, a patient group in whom clinical benefit has previously been reported[13,14].

Enlarged lymph nodes (<1 cm diameter) could be differentiated into those which contained tumour deposits and those which did not by their uptake of radioactivity relative to normal colon. This suggests that this may be a useful method of detecting nodal metastases in the field of resection of a colorectal cancer. The deposits localized (<1 cm diameter) are smaller than those commonly seen on γ-camera imaging

Table 4 *Results for the CdTe probe with parallel hole collimator and a 100 s counting period*

'Tumour' size (ml)	'Tumour' to background ratio			
	2:1	4 1	6.1	8.1
0·5	−1·10	1·29	2 31	4·04*
1 0	1 52	4 01*	4·52*	3 28*
1·5	1 36	4 04*	1 86	6 29*
2 0	−0 55	4·27*	6 18*	8 74*
5 0	1·83	6·28*	11·53*	11 35*
10 0	3 17*	7 64*	13·42*	19 08*

The results shown are the number of standard deviations between the mean counts over the 'tumour' to that over background; *more than three standard deviations

Table 5 *Minimum 'tumour' sizes (in ml) detectable*

	NaI		CdTe (w.a)		CdTe (p.h)	
Ratio	20 s	100 s	20 s	100 s	20 s	100 s
2:1	10 0	5 0	None	None	None	10 0
4 1	1·5	0 5	10 0	5 0	10·0	1 0
6 1	1·5	0 5	5·0	1 0	5 0	1 0
8:1	1 0	0 5	1·0	0·5	1 0	0 5

The minimum 'tumour' sizes detectable are based on a level of detectability of three standard deviations. Figures are for 20 s and 100 s counting periods w a , Wide angle collimator; p h , parallel hole collimator using ^{111}In-MAb and this supports the use of radiation-detecting probes intraoperatively in addition to external γ-camera imaging for localizing cancer deposits with radiolabelled antibodies[9,10].

No liver metastases were localized with this technique due to the uptake of activity by normal liver parenchyma. This situation may be altered by the use of a radionuclide which is cleared by the normal liver such as radioiodine, which undergoes rapid tissue dehalogenation and excretion[25].

Despite many clinical studies having been carried out on intraoperative probing with radiolabelled antibodies, this technique has not previously been adequately assessed. The design of the experimental model allowed careful investigation of its potential and limitations. The results suggest that intraoperative probing may allow the detection of tumour deposits as small as 1·5 ml at a tumour to background ratio of 4:1 (NaI probe) and 1 ml at an 8:1 ratio (both probes) with a counting period of 20 s. This size of tumour deposit may easily be overlooked by an operating surgeon either at a resection of a primary cancer or at second look laparotomy and this may alter the prognosis for the patient involved. Although high uptake ratios are required for the reliable detection of small tumour deposits, this uptake is in the range which has been reported from human studies[26].

The accuracy of the experimental model is dependent on the variables on which it is based, particularly on the percentage of the injected dose taken up by the tumour tissue. This dosage was based on the findings of the present clinical study with ^{111}In-ICR2 in colorectal cancer patients and is in agreement with other studies on the clinical use of radiolabelled MAbs in cancer patients[25]. Many clinical studies using radiolabelled antibodies have not, however, quoted the tumour uptake as a percentage of the injected dose or the ratio of tumour uptake to that of normal colon and may therefore produce better or worse results than those determined from the present study. Another factor to be considered when evaluating the clinical correlation of the present model is that in patients the tumour does not lie within a homogeneous background of activity but in proximity to non-tumour sites of high ^{111}In-MAb uptake such as the liver, spleen and bone marrow. The liver may be responsible for the uptake of up to 30–40 per cent of the injected dose of ^{111}In-labelled antibody[35] and this would therefore produce considerably higher background counts and a lower T/NC difference in counts when probing in its vicinity. Similarly the pelvis and retroperitoneal tissues are common sites of recurrent colorectal cancer and the results of intraoperative probing in this area will be influenced by the uptake in the bony pelvis and lumbar vertebrae. The results obtained *in vivo*, therefore, may not reach those in the present model.

Of the two probes studied the NaI detector was more sensitive and therefore able to detect smaller tumour deposits at any given tumour to background ratio than the CdTe probe. This is partly due to the physical size of the probes, the NaI being considerably larger than the CdTe and containing a much larger detector. Due to its lead shielding the NaI probe has the disadvantage of being heavy and difficult to manoeuvre at operation whilst its crystal detector is sensitive to rapid temperature changes and requires to operate at a high voltage. The CdTe semiconductor probe, on the other hand, is light, easily sterilizable, robust and is a self-contained rechargeable battery powered unit It is therefore more suited for intraoperative probing. Increasing the crystal thickness of the CdTe probe may improve the detectability of small tumour deposits at low tumour to background ratios.

The statistical analysis of the tumour and background counts used in the present phantom study represents a significant advance over the system presently used clinically which is based on an arbitrarily defined cut-off level of 1·5:1 for tumour to background counts[13]. Although easily applied in a clinical situation, the statistical significance of this ratio of counts will depend on the actual number of counts on which it is based and will therefore vary with the half-life of the radionuclide used, the rate of tumour uptake and clearance of radiolabelled antibody, and the period between administration and intraoperative probing. The application of statistical analysis to the counts obtained in the clinical situation would allow the significance of the total counts and difference between tumour and background to be calculated Taking three standard deviations as a level of significance would result in less than a 1 per cent chance that the difference in counts is due to random error rather than a true difference in the level of uptake.

This application of counting statistics is a method of optimizing the information presently available in clinical studies. This may not be necessary if a more specific MAb was developed or the non-specific uptake of labelled MAbs avoided. Until this is achieved other techniques could be employed to improve the tumour to background count ratio, such as the blocking of background uptake with unlabelled specific antibody or clearing circulating activity following tumour localization using a second antibody directed against the first[38,39]. Another alternative may be to allow the background radioactivity to clear spontaneously by using a radionuclide with a long half-life or to adminster the antibody and radionuclide separately linked to the high affinity avidin and biotin[40,41].

In conclusion, the intraoperative probing of radiolabelled monoclonal antibodies shows promise for the localization of small tumour deposits which may not be detected by other means. Its routine use as a clinical technique, however, is unlikely at present due to the complex procedures required for its optimization.

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Suture technique affects perianastomotic colonic crypt cell production and tumour formation

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Suture line recurrence is an important cause of failure after potentially curative resection for colonic carcinoma. Our aim was to determine whether suture technique affected the incidence of perianastomotic tumours in experimentally induced colonic cancer. Sprague–Dawley rats were randomized into three groups. A 1 cm longitudinal colotomy was repaired with four interrupted 6/0 polypropylene monofilament sutures, using either a transmural technique ($n = 18$) *or a seromuscular technique* ($n = 18$)*. Control animals* ($n = 18$) *had a sham laparotomy. All animals received nine, weekly, subcutaneous injections of azoxymethane (total dose 90 mg/kg) starting 6 weeks after laparotomy. Surviving animals were killed 32 weeks after laparotomy. Five animals from each group were given intraperitoneal bromodeoxyuridine (100 mg/kg) 1 h before being killed. At death, perianastomotic tumours occurred more frequently in animals with transmural sutures than in either controls or those with seromuscular sutures. This difference was associated with a greater mucosal bromodeoxyuridine crypt cell labelling index in the transmural suture group. We conclude that a transmural anastomotic suture technique promotes the development of experimental perianastomotic colonic tumours.*

Local recurrence is an important cause of failure after potentially curative colonic resection for carcinoma. The incidence is reported to be in the region of 15 per cent[1–4]. In the majority of cases a salvage procedure is not feasible[5]. Anastomotic recurrence may be caused by incomplete primary resection or the implantation of viable exfoliated tumour cells[1,6,7]. In 30 per cent of cases anastomotic recurrence occurs late (two or more years after primary resection) and may be caused by metachronous carcinogenesis[1,8]. It has been suggested that anastomoses produce areas of instability in colonic mucosa and so predispose to metachronous tumour formation[1,9]. This hypothesis has been the subject of considerable animal research, much of which has focused on the influence of suture material on the incidence of experimentally induced colonic cancer[7,10–14]. Very little information exists on the effect of anastomotic technique on metachronous perianastomotic tumour formation. Seromuscular sutures do not traverse the colonic mucosa and so may induce less mucosal reaction than conventional full thickness sutures. It was our hypothesis that a seromuscular suture technique might reduce the incidence of experimentally induced perianastomotic tumours when compared with a conventional full thickness suture technique.

Materials and methods

Suture placement

A preliminary study was performed to confirm the accuracy of suture placement. Ten 6-week-old male Sprague–Dawley rats were anaesthetized using intraperitoneal injections of pentobarbitone. A 1 cm longitudinal colotomy was made in the antimesenteric wall of the distal colon. Using an operating microscope, the colotomy was repaired using four interrupted 6/0 polypropylene monofilament sutures. In four animals a transmural suture technique was used, and a seromuscular technique was used in the remaining six animals. The abdominal wall was closed using continuous 3/0 monofilament polyamide sutures. The animals were allowed to recover, fed a standard rat chow diet and allowed water *ad libitum*. The animal quarters were lit in alternate 12 h cycles and the temperature was maintained at 20°C. The animals were killed 6 weeks after laparotomy using carbon dioxide narcosis. The area of the anastomosis was excised and preserved in 10 per cent phosphate buffered formaldehyde for histological examination. Multiple histological sections through the site of anastomosis were examined by a histopathologist (D.R.) who was unaware of the suturing technique used. In each case the suture tracts were sought and judged to have been either seromuscular or transmural.

Tumour induction study

In this study 54 male Sprague–Dawley rats 6–8 weeks old were randomized into three groups. Under pentobarbitone anaesthesia and using the surgical techniques described, a 1 cm longitudinal colotomy in the distal colon was repaired using either a transmural suture technique (group 1, $n = 18$) or a seromuscular suture technique (group 2, $n = 18$). Control animals (group 3, $n = 18$) had a sham laparotomy with massage of the distal colon for 5 min to simulate the effect of tissue manipulation[7,15]. The animals were allowed to recover and were maintained under the conditions described, three rats per cage, one from each group. Six weeks after laparotomy all animals received the first of nine, weekly subcutaneous injections of the carcinogen azoxymethane at a dose of 10 mg/kg. All surviving animals were killed 32 weeks after laparotomy using carbon dioxide narcosis. Five rats from each group were selected at random to receive an intraperitoneal injection of 100 mg/kg bromodeoxyuridine (BrdU) 1 h before being killed. BrdU is incorporated into DNA during the S phase of mitosis[16]. This technique provides a measure of epithelial mitotic activity through measurement of the BrdU crypt cell labelling index[17,18].

At autopsy, the entire colon was excised from each animal, opened along the mesenteric border and washed in water. The number, site and macroscopic appearances of all colonic tumours were recorded. A careful search was made for suture material at the colotomy site, and the number of residual sutures were noted. The specimens were preserved in 10 per cent phosphate buffered formaldehyde. All tumours and the distal 5 cm of colon, which included both the anastomotic site and the area of massage, were prepared for histological examination by standard techniques. Sections were stained with haematoxylin and eosin. Histological sections of perianastomotic mucosa that had been exposed to BrdU were stained using an immunohistochemical technique. Dewaxed sections were incubated with monoclonal mouse anti-BrdU antibody (Becton-Dickinson, Oxford, UK) and then with peroxidase conjugated rabbit antimouse antibody (Dakopatts Ltd, High Wycombe, UK). Peroxidase staining was completed using

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diaminobenzidine and sections were lightly counterstained with haematoxylin. The slides were coded and examined by one of the authors who was unaware of the code. The BrdU labelling index was calculated as the ratio of BrdU labelled nuclei to the total number of crypt nuclei. Only crypts cut through the longitudinal axis were considered, and the index was expressed as the mean of 20 crypt columns[17,18].

Statistics

Comparisons of tumour incidence and distribution in the three study groups were made using χ^2 analysis. Comparisons of the BrdU labelling index between the three groups was made using Student's *t* test after initial analysis of variance.

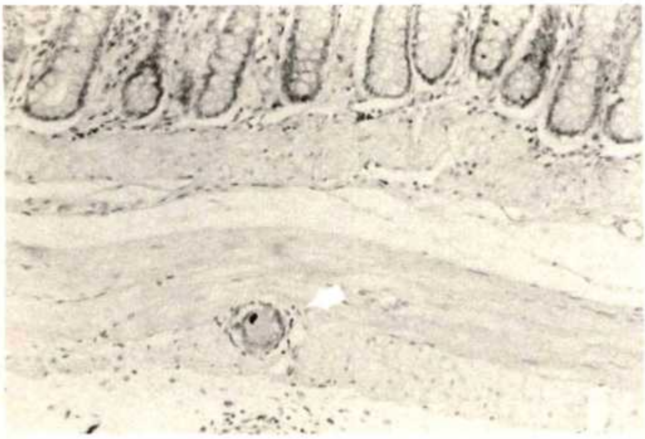

Figure 1 *Histological preparation showing a seromuscular suture tract (arrow). (Haematoxylin and eosin, original magnification × 10)*

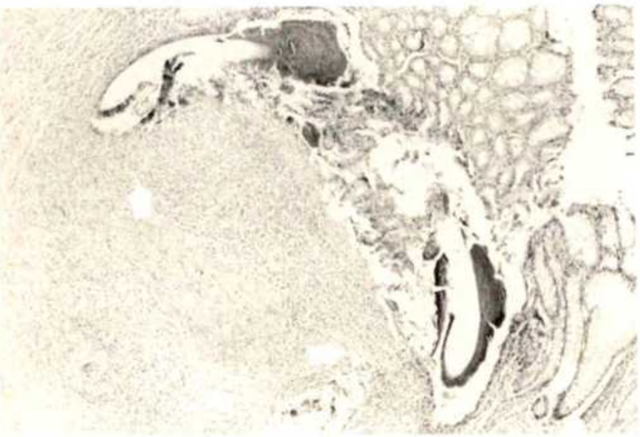

Figure 2 *Histological preparation showing a transmural suture tract (arrows). (Haematoxylin and eosin, original magnification × 10)*

Results

In the suture placement study, histological examination of the anastomosis confirmed the presence of seromuscular suture tracts in four of six animals (*Figure 1*). The presence of transmural suture tracts was confirmed in three of four animals (*Figure 2*). In the three remaining animals it was not possible satisfactorily to identify the suture tract and the examination was deemed inconclusive. In no case was there an incorrect determination of anastomotic technique.

There were ten peroperative or early postoperative deaths during the 32-week tumour induction study. None was due to the development of colonic cancer. Colonic carcinoma, single or multiple, developed in 55 per cent of animals surviving to the end of the study. Tumours occurred more frequently in the region of the colotomy repair than in control animals (*Figure 3*). More animals developed perianastomotic tumours when the transmural suture technique was used (group 1) compared with the seromuscular suture technique (group 2). Perianastomotic tumours were more frequently multiple in group 1 than in group 2 (*Table 1*).

The BrdU labelling index was greater in perianastomotic mucosa than in control mucosa. Furthermore, the BrdU index was greater in the transmural suture group (group 1) than in the seromuscular suture group (group 2), a finding consistent with the observed incidence of perianastomotic tumours (*Table 1*).

In the preliminary study all anastomotic sutures were present at death 6 weeks after insertion. However, in the tumour

Table 1 *Incidence of cancers and results of bromodeoxyuridine (BrdU) labelling of perianastomotic colonic mucosa in group 1 (transmural suture), group 2 (seromuscular suture) and group 3 (control)*

	Group 1 ($n=18$)	Group 2 ($n=15$)	Group 3 ($n=11$)
No. of rats with anastomotic tumours*	11	5	0
No. of anastomotic tumours†	16	5	0
No. of tumours in remaining colon	6	8	5
Mean BrdU labelling index (s.e.m.)‡	22 (1)	16 (1)	13 (1)

* $\chi^2 = 11\cdot11$, $P < 0\cdot005$; group 1 *versus* group 2 *versus* group 3
† $\chi^2 = 3\cdot98$, $P < 0\cdot05$; group 1 *versus* group 2
‡ Group 1 *versus* group 2, $P < 0\cdot05$; group 1 *versus* group 3, $P < 0\cdot001$, group 2 *versus* group 3, $P < 0\cdot005$ (Student's *t* test)

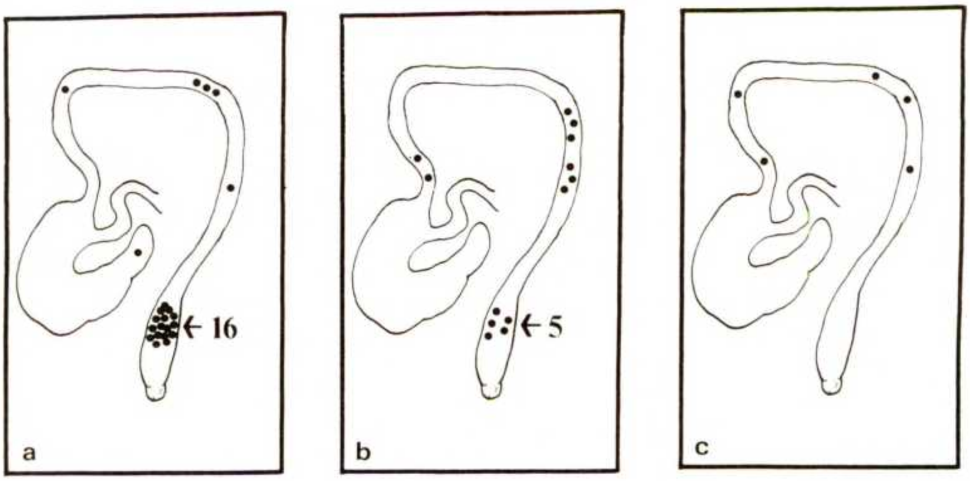

Figure 3 *Distribution of colonic cancers in:* **a** *group 1, transmural sutures;* **b** *group 2, seromuscular sutures; and* **c** *group 3, controls*

induction study, only five of 72 transmural sutures remained, although 59 of 60 seromuscular sutures were identified 32 weeks after insertion.

Discussion

Experimentally induced colonic tumours preferentially develop in the region of an anastomosis[1,9]. The central importance of crypt cell production to the susceptibility of colonic mucosa to carcinogens is demonstrated by the effect of factors that alter crypt cell production on perianastomotic tumour formation. Thus small bowel resection[19,20] and exposure to high levels of bile salts[21,22], which increase colonic crypt cell production, also increase experimental colonic tumour formation. On the other hand, diversion of the faecal stream[23] and dietary supplementation with calcium[24], which decrease crypt cell production, also decrease experimental colonic cancer formation. It may be inferred that the colonic crypt cell proliferation which accompanies anastomotic healing induces mucosal instability, thus rendering colonic mucosa more susceptible to the effects of carcinogens[1,9,19,20]. Healed anastomoses are also preferential sites for the development of experimental colorectal cancers[25], even though it has been shown, using tritiated thymidine, that colonic crypt cell production returns to normal 6 weeks after mucosal injury[26]. Simple surgical injury, with subsequent healing, is not sufficient to explain this susceptibility.

These observations have led several investigators to examine the effects of different suture materials on crypt cell production and perianastomotic cancer formation. It has been found that braided and non-absorbable sutures are associated with greater crypt cell production and more perianastomotic tumours than monofilament and absorbable sutures[7,12,13,25]. We have extended these observations by demonstrating that transmural sutures excite more long-term crypt cell proliferation at an anastomosis than seromuscular sutures. This difference is reflected in a higher incidence of experimentally induced perianastomotic colon cancers in animals with transmural sutures.

The present results are of considerable clinical interest given the wide variation of techniques of colonic anastomosis among surgeons. A two-layer technique using mucosal absorbable and seromuscular non-absorbable suture material is conventional, although many surgeons prefer a single-layer transmural anastomosis using non-absorbable suture material[27]. A single-layer seromuscular anastomotic technique using non-absorbable suture material has been advocated, based on the rationale that less inversion occurs and therefore anastomotic stenosis is less likely[28]. The present data suggest that use of this technique may also decrease mucosal instability in the region of the anastomosis and be associated with a lower incidence of metachronous perianastomotic tumours.

These results may also reflect a lower propensity for perianastomotic tumour development in conventional two-layer colonic anastomoses. Chromic catgut in the mucosal layer of an anastomosis may be expected to be absorbed 6 weeks after operation[29]. Thus chromic catgut is unlikey to affect the suceptibility of perianastomotic mucosa to neoplastic change in response to carcinogen exposure. Indeed, chromic catgut has been shown to be the only suture material not to influence the site of dimethylhydrazine-induced experimental colonic tumours[12].

The results of this study cannot be explained on the basis of long-term persistence of sutures at the site of anastomosis. Unexpectedly, we found that only 7 per cent of transmural sutures remained at the anastomosis 8 months after construction, whereas 98 per cent of seromuscular sutures were still present. Yet it was the transmural group which had the greater crypt cell labelling index and higher number of perianastomotic tumours. As shown in the preliminary validation study, all sutures were probably present at the time of tumour induction. Phillips and Cook[7] found that 15 per cent of transmural steel wire sutures persisted at an anastomosis 10 months after construction compared with only 4 per cent of transmural silk sutures. Based on these observations they suggested that non-absorbable sutures, especially steel wire or staples, should be avoided when constructing a large bowel anastomosis. Although we have not compared absorbable with non-absorbable sutures, the present data suggest that large bowel anastomoses can be safely constructed with non-absorbable monofilament sutures and that a seromuscular suture technique is to be preferred.

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Short note

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Clinical presentation of dracontiasis

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Guinea worm infestation, dracontiasis, causes much debility in many rural areas of Nigeria, especially Cross River State.

Dracunculus medinensis is the causative organism of dracontiasis which is transmitted by drinking water infested with a crustacean, cyclops, which harbours the larvae of the parasite. In the human digestive system, enzymes destroy the cyclops, releasing the larvae which migrate through tissues until they become mature[1]. After copulation the male worm dies while the female migrates to the subcutaneous tissues of the lower extremities[2]. The worm provokes the formation of a boil which blisters, and later a punctum or ulcer through which the anteriorly placed opening of the uterus discharges millions of embryos on contact with water. When all the embryos have been discharged the female worm dies. The usual lesions of dracontiasis are blisters, boils, ulcers and abscesses mostly in the lower extremities[1–3]. However, in hyperendemic districts where the infestation rate is high and little or no treatment is available the ultimate clinical picture of the disease becomes evident.

Patients and method

One hundred patients were randomly selected from the village of Ofadua in Cross River State of Nigeria for study.

The age, sex, site of lesion, type and nature of lesion, number of lesions, local and constitutional effects of the lesion and effect of treatment were documented. The village was visited twice weekly.

Both the study group and other patients were treated in a nearby health centre with oral doses of metronidazole 400 mg thrice daily for 1 week and albendozole 400 mg daily for 3 consecutive days. The ulcers were cleaned with Savlon (ICI Pharmaceuticals) while the guinea worms were coiled around match sticks to encourage their extrusion. The more serious cases were referred to the nearest district hospital.

Results

All 100 patients had guinea worm lesions distributed throughout the body (*Table 1*). A lesion was found in the spinal cord producing paraplegia. Lesions were also found on the breast in one patient, on the trunk producing intramuscular abscess in ten patients, and multiple cutaneous nodules were found in 13 patients (*Figure 1*). Genital lesions consisted of a scrotal abscess and orchitis.

Lesions of the lower extremities included blisters in 60 patients, ulcers in 58 patients, cellulitis in 28 patients, oedema in 25 patients, boils in 20 patients, arthritis in 10 patients and pyomositis in 5 patients.

Ten cases presented with abnormalities of gait ranging from staggering gait and broad-based gait to crawling owing to severe widespread lesions of the lower extremities. Constitutional disturbance was minimal. Male to female ratio was 1:1.

Table 1 *Clinical presentation of dracontiasis in 100 patients in a hyperendemic district*

Clinical features	No. of cases
Head and neck	
Proptosis	2
Glossitis	2
Parotitis	2
Central nervous system	
Paraplegia	1
Breast lesion (mastitis)	1
Trunk	
Pyomyositis/intermuscular abscess	15
Multiple cutaneous nodules	13
Boils	2
Genital lesions	
Scrotal abscess	1
Orchitis	1
Lower extremities	
Blisters	60
Ulcers	58
Cellulitis	28
Oedema	25
Boils	18
Disordered gait	10

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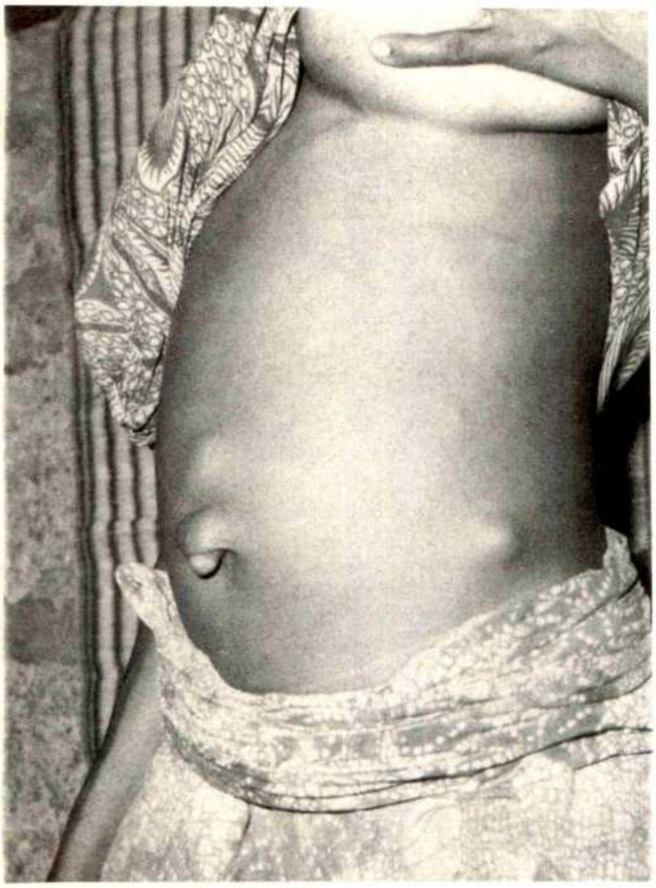

Figure 1 *Cutaneous nodules of dracontiasis. Painful cutaneous nodules simulating Dercum's adiposo dolorosa*

Discussion

Classical textbook descriptions of lesions of dracontiasis are boils, blisters, ulcers and abscesses distributed mostly in the lower extremities. Thus sporadic cases reported at other sites are regarded as aberrant lesions. The impression is thus created that dracontiasis can be treated conservatively with drugs and dressing of ulcers and only on rare occasions is the attention of the surgeon required. In a hyperendemic district such as the one under study where more than 70 per cent of the entire population are heavily infested throughout the year, lesions at other sites hitherto regarded as aberrant lesions become so frequent as to be regarded as the normal clinical presentation of the disease.

Lesions have been described in the brain, spinal cord, placenta, pericardium, kidneys, bladder and joints, leading to brain abscess, paraplegia, abruptio placentae, constrictive pericarditis, renal or bladder abscess and purulent arthritis respectively[2–11]. In this study, lesions were also found in the orbit, tongue, parotid gland, breast, scrotum, testis and spinal cord, all of which required expert surgical treatment.

The aberrant lesions produce diagnostic difficulties to the unwary clinician; for example, heterotopic calcification from calcium deposition in dead worms in the pelvis, muscle, brain, etc. produce gastrointestinal and neurological symptoms[11–13]. Cutaneous nodules may be confused with lipoma, onchocercoma, neurofibroma, fibroma, or even tuberculoma, or an enlarged lymph node when they occur in the groin or axilla. Finally, secondary infection may lead to pyogenic abscesses, pyogenic arthritis, lymphangitis, lymphadenopathies and tetanus[2–14].

Dracontiasis is thus a surgical disease which presents with lesions throughout the body when the infestation rate is high, and lesions restricted mostly to the lower extremities when the infestation rate is low.

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Pyoderma gangrenosum in inflammatory bowel disease

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Since 1954, 34 patients have attended St. Mark's Hospital with pyoderma gangrenosum in association either with ulcerative colitis (22 patients) or Crohn's disease (12 patients). Lesions were multiple in 71 per cent and over half were situated below the knees. Ulcerative colitis was active in 11 patients (50 per cent) and Crohn's disease was active in nine (75 per cent) when pyoderma gangrenosum was diagnosed. Associated illnesses – most commonly a seronegative arthritis affecting large joints – were present in 55 per cent and 92 per cent of cases respectively. A diffuse pustular rash appeared in six patients, synchronously with pyoderma in five. In a further seven patients (two with ulcerative colitis, five with Crohn's disease) the onset or course of pyoderma might have been linked to the presence of non-dermatological suppuration. Pyoderma resolved without intestinal resection in two-thirds of patients. When present at the time of surgical resection (15 procedures in 13 patients), pyoderma healed promptly in six cases, only with additional therapy in four cases and very slowly or not at all in five cases. Pyoderma gangrenosum occurs in both ulcerative colitis and Crohn's disease. Healing after intestinal resection is unpredictable both with respect to timing and extent of resection.

Pyoderma gangrenosum is a painful, chronic, ulcerating skin disease of unknown cause. It commences as an erythematous papulopustule and rapidly evolves to form an area of frank ulceration with undermined, violaceous edges and a bright outer halo of erythema. Diagnosis is clinical, there being no accepted histological diagnostic criteria. It may be secondary to a vasculitis[1].

An underlying systemic illness is present in more than 75 per cent of patients. Inflammatory bowel disease, either ulcerative colitis or Crohn's disease, is the most frequent, being present in 30–40 per cent[2]. Pyoderma will develop in 0·5–5 per cent of patients with inflammatory bowel disease[2–5].

Skin activity is said to parallel intestinal activity and to be cured by excision of all diseased intestine[2,6–8]. Pyoderma gangrenosum may precede the onset of inflammatory bowel disease[3]; run a course independent of intestinal disease activity[9,10]; respond poorly to intestinal resection[4]; and develop years after total proctocolectomy for ulcerative colitis[11,12]. This report deals with patients with pyoderma gangrenosum and either ulcerative colitis or Crohn's disease seen at one hospital.

Patients and results

Patient groups (Table 1)

Since 1954 34 patients with a clinical diagnosis of pyoderma gangrenosum associated with ulcerative colitis (22 patients) or Crohn's disease (12 patients) have been seen at this hospital. All case notes were reviewed, additional information being sought from patients or referring physicians by questionnaire.

Response to treatment (Table 2)

Medical therapy in ulcerative colitis always involved systemic steroids, whereas in Crohn's disease steroids were administered to five patients, the others healing with azathioprine[1], topical steroids[1], or spontaneously[1].

Two patients with ulcerative colitis and one with Crohn's disease had residual diseased intestine: in one, pyoderma gangrenosum healed promptly after operation.

Intestinal disease was symptomatically inactive in four patients who had ulcerative colitis and who underwent resection: the skin lesion healed promptly in two, with the aid of a split skin graft in one and very slowly in the other.

Distant suppuration (Table 3)

An unexpected association between the development and persistence of pyoderma gangrenosum and the presence of a focus of non-dermatological cutaneous suppuration was noted in seven patients.

Discussion

This report of 34 cases of pyoderma gangrenosum in inflammatory bowel disease is the largest to date. Pathergy, the tendency for pyoderma to develop at the site of previous skin trauma, occurred in 12 per cent of cases (reported range 10–27 per cent[2,3]); the lower legs were most often affected[2]; and multiple lesions were common (ulcerative colitis 73 per cent, Crohn's disease 67 per cent).

Associated systemic illness was particularly likely in Crohn's disease (11 of 12 patients). Pyoderma gangrenosum and seronegative large joint arthritis, as occurred here in 14 patients, may be seen together even in the absence of inflammatory bowel disease[2,13].

In one previous report of 42 patients with ulcerative colitis and associated skin diseases[3], erythema nodosum and pyoderma gangrenosum were diagnosed only once in the same patient, whereas there are nine patients described here with this combination (26 per cent).

Diffuse pustules form in patients with pyoderma gangrenosum[6], as seen here in six patients, and hidradenitis suppurativa and acne conglobata may also be associated[2]. In seven patients there seemed to be an association between the development and persistence of pyoderma gangrenosum and the presence of a focus of distant suppuration. This association may be entirely coincidental as deep sites of sepsis and perianal sepsis are not uncommon in patients with inflammatory bowel disease. However, there is theoretical support: cross-antigenicity between *Escherichia coli* and cutaneous antigens might explain the successful treatment of previously unresponsive pyoderma gangrenosum in two patients by selective elimination of *E. coli* from the gastrointestinal tract[14]. Furthermore,

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Table 1 *Clinical details of 34 patients with pyoderma gangrenosum in association with ulcerative colitis and Crohn's disease*

	Ulcerative colitis		Crohn's disease	
Sex distribution (M:F)	8:14		6.6	
Median(range) age at onset of pyoderma gangrenosum (years)	32 (15–77)		27·5 (16–56)	
Extent of intestinal disease at onset of pyoderma gangrenosum	Total colitis	12	Anus only	1
	Left-sided colitis*	8	Anus + large bowel	6
	Rectum after colectomy + ileorectal anastomosis	2	Colon only	2
			Ileum + colon	2
			Mouth only†	1
Intestinal disease symptomatically active at onset of pyoderma gangrenosum	11‡ (50%)		9§ (75%)	
Number of skin lesions (single·multiple)	6 16		4 8	
Sites of skin lesions				
Legs (below knee)	26		16	
Thighs/buttocks	10		3	
Upper limbs	2		3	
Chest/back	6		–	
Head and neck	3		1	
Peristomal/wound	2		1	
History of pathergy¶	3		1	
Associated illnesses	12 (55%)		11 (92%)	
Seronegative arthritis	5		9	
Erythema nodosum	4		5	
Iritis/episcleritis	3		6	
Oral ulceration	2		3	
Pustular rash	3		3	
Abscess at distant site	2		5	

* Distal to splenic flexure on radiology; † confirmed by biopsy of oral ulcer; ‡ seven had total colitis, three had left-sided colitis and one had rectal involvement after colectomy and ileorectal anastomosis; § of the three patients with inactive disease at the onset of pyoderma gangrenosum, one had oral ulceration only, one had anal and perianal disease with no involvement of colorectal mucosa, and the third had recurrent ileal disease with minimal colonic ulceration after an earlier right hemicolectomy; ¶ ulceration developing at the site of previous skin trauma (including surgical incisions and stomal margins)

Table 2 *Response to treatment of pyoderma gangrenosum*

	Ulcerative colitis	Crohn's disease
Pyoderma gangrenosum healed with medical therapy	15 (68)	8 (67)
Intestinal resection when pyoderma gangrenosum present	9*	6†
Response to resection		
Prompt healing	3	3
Healing only with additional therapy	3‡	1§
Unhealed or very slow healing	3	2
Recurrent episodes of pyoderma gangrenosum (all treatments)	8 (36)	5 (42)

Values in parentheses are percentages; * nine resections in eight patients; † six resections in five patients; ‡ steroids required in two, split skin graft in one, § steroids required

epidermolytic proteases can be found in the stools of patients with pyoderma gangrenosum[15]: presumably the antigen responsible is intestinal. In this series, in nine out of 12 patients with Crohn's disease, whose pyoderma gangrenosum and intestinal disease activity were associated, the Crohn's disease was colonic. Pus was obtained from only two of the seven patients with distant sepsis (pelvic abscess in patient no. 1, purulent peritonitis in patient no. 6), and *E. coli*, along with a number of other organisms, was grown.

Pyoderma often healed without the need for surgery[3,4] but when an operation was performed healing was unpredictable; neither intestinal disease activity (contrary to one other report[4]) nor 'curative' resection – proctocolectomy for ulcerative colitis or complete resection of macroscopically involved bowel for Crohn's disease – seemed to make any difference. One patient remained unhealed more than 1 year after proctocolectomy for ulcerative colitis and had recurrence at a new site 4 years later.

The nature of the association between pyoderma and inflammatory bowel disease is unclear Both appear to belong to a family of diseases along with arthritis and erythema nodosum which may have common immunological mediators[2]. Large bowel involvement is common in patients with pyoderma and Crohn's disease, both in this and other series[5,16], so the colon may be the source of these common mediators.

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Table 3 *Association of pyoderma gangrenosum with distant suppuration*

Patient no.	Underlying inflammatory bowel disease	Clinical summary
1	Ulcerative colitis	Unsuspected, large pelvic abscess found at proctocolectomy Pyoderma gangrenosum healed promptly after surgery
2	Ulcerative colitis	Left-sided colitis with rectovaginal fistula and extensive perianal suppuration at onset of pyoderma gangrenosum. Pyoderma gangrenosum remained unhealed until perineal sepsis was controlled 2 months after proctocolectomy
3	Crohn's disease	Multiple perianal and enterocutaneous fistulae at onset of pyoderma gangrenosum Proctocolectomy allowed pyoderma gangrenosum to heal. Recurrence of pyoderma gangrenosum 6 months later while asymptomatic, resistant to medical therapy for 16 months until spontaneous perineal discharge of enterocutaneous fistula with prompt resolution of pyoderma gangrenosum
4	Crohn's disease	Distal large bowel disease only. Onset of pyoderma gangrenosum associated with multiple perianal fistulae and discharge of pus *per rectum* Rectal excision complicated by further perineal sepsis, pyoderma gangrenosum on leg healed but new lesion appeared around stoma, remaining unhealed at that site until perineal suppuration was controlled 4 months after proctectomy
5	Crohn's disease	Severe anorectal disease with groin and perianal Crohn's ulceration and pus discharging *per rectum* at onset of pyoderma gangrenosum Prompt healing of pyoderma gangrenosum followed *per-rectal* drainage of a large perirectal abscess
6	Crohn's disease	Flare-up of known total colitis associated with rectovaginal and anal fistulae at onset of pyoderma gangrenosum. Pyoderma gangrenosum healed in 2 weeks with topical dapsone and azathioprine Re-presented 4 weeks later with purulent peritonitis secondary to a ruptured pericolic abscess
7	Crohn's disease	Colonic disease associated with recurrent pyoderma gangrenosum treated by colectomy and ileorectal anastomosis. Further exacerbation of pyoderma gangrenosum 4 months before a rectovaginal fistula developed Small bowel found to be entirely normal at laparotomy for concurrent small bowel obstruction Pyoderma gangrenosum healed but reappeared 12 months later at a different site in association with a dental abscess and septic arthritis but no evidence of intestinal disease

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Strategy for management of distal ileal Crohn's disease

We have determined the outcome of a defined policy for the management of distal ileal Crohn's disease using a prospective computer-based analysis of 139 patients diagnosed between 1970 and 1988 with a mean follow-up of 10 years. The policy in outline consists of conservative treatment for acute obstructive episodes, resection or strictureplasty for recurrent obstructive episodes, surgical treatment for abscess and fistula formation and specific medical treatment (corticosteroids, immunosuppressive therapy or metronidazole) for symptomatic non-obstructive disease. Twenty-nine patients had a benign course without resection. The remainder were treated surgically at some time but only 28 of these patients had specific treatment before operation. Thirty-three needed more than one resection and five needed more than three surgical procedures. Immediate, early or delayed surgical treatment did not affect the reoperation rates or the long-term outcome. Eleven patients died, ten of causes unrelated to Crohn's disease. Of the 128 living patients, 114 are fit and well, and only two are currently taking specific medication. Fourteen are unwell of whom six either need or have refused further surgery which could restore them to good health. This management policy has achieved excellent long-term results in nearly all patients, and our findings suggest that the timing of surgery and its nature are more important in determining outcome than specific medical therapy.

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Crohn's disease involving the distal ileum is common and much has been written about its symptoms, signs, complications and short-term response to medical therapy. There have been few studies of the long-term natural history. Lennard-Jones and Stalder described the long-term outcome in 73 patients with distal ileal Crohn's disease and calculated annual reoperation rates for recurrent disease[1]. Truelove and Pena studied the course and prognosis of 221 patients with Crohn's disease at the Radcliffe Infirmary, Oxford between 1938 and 1970. The purpose of this report was an analysis of the difference in outcome between primary and referred cases; the prognosis of distal ileal disease was not considered in detail[2]. Epidemiological studies from Copenhagen[3] and Stockholm[4] have analysed many aspects of the outcome of Crohn's disease but have not specifically addressed the natural history of distal ileal disease.

An earlier study from our unit reported operation and reoperation rates and the long-term outcome of distal ileal disease among 227 patients with distal ileal Crohn's disease under long-term review between 1944 and 1978. This study showed that the excess mortality was higher in the early years of our experience and that the introduction of more conservative surgery had improved the outcome[5].

A consistent management policy was developed in this earlier study and has been used since in the care of patients with Crohn's disease The policy includes evaluation of the symptomatic patient to define the site and extent of disease and the detection or exclusion of complications such as stricture formation, abscess or enterocutaneous fistula. Disease activity is assessed regularly by measurement of haemoglobin, serum albumin and acute phase proteins. The management policy includes the treatment of obstructive episodes with intravenous fluids and nothing by mouth for a few days, but no specific medical therapy. Most patients with symptomatic ileal Crohn's disease already have a narrowed, thickened segment of bowel at the time of diagnosis. Recurrent obstructive episodes, usually three or more, are considered an indication for resection or strictureplasty. An abscess or fistula is an indication for surgical treatment. No treatment is prescribed for the asymptomatic patient even with gross radiological evidence of Crohn's disease Short courses of sulphasalazine or 5-amino-salicylates are prescribed for the mildly symptomatic patient particularly with diarrhoea. Specific medical treatment in this context includes corticosteroids, immunosuppressive therapy and metronidazole. Short courses of corticosteroids are prescribed for symptomatic patients considered to have active distal ileal Crohn's disease. (A few patients with established Crohn's disease when first referred to this unit had already received prolonged courses of corticosteroids or immunosuppressive therapy.) Metronidazole is used occasionally for treatment of associated perianal disease.

Recent modifications of this management policy include the routine use of perioperative antimicrobial prophylaxis, the more frequent use of conservative surgery (strictureplasty when appropriate rather than resection) and the nutritional support of malnourished patients with enteral or parenteral feeding.

This study was established to determine the long-term outcome among a large series of patients with distal ileal disease in whom this management policy had been applied prospectively.

Patients and methods

One hundred and thirty-nine patients with distal ileal Crohn's disease (63 men, 76 women) diagnosed between 1970 and 1988 were reviewed. Of these, 84 patients were first seen in this unit and 55 were referred from other gastroenterologists. Only 17 of the 84 patients (20 per cent) with distal ileal Crohn's disease first seen in our unit had received corticosteroids and none had received immunosuppressive therapy or total parenteral nutrition. On the other hand, 30 of the 55 patients (55 per cent) referred had received corticosteroids, three azathioprine and five total parenteral nutrition. Once referred, patients were treated using the guidelines outlined in the management policy

The mean age at diagnosis was 32·2 years (range 13–93 years) with a mean interval from onset of symptoms to diagnosis of 2·9 years (range

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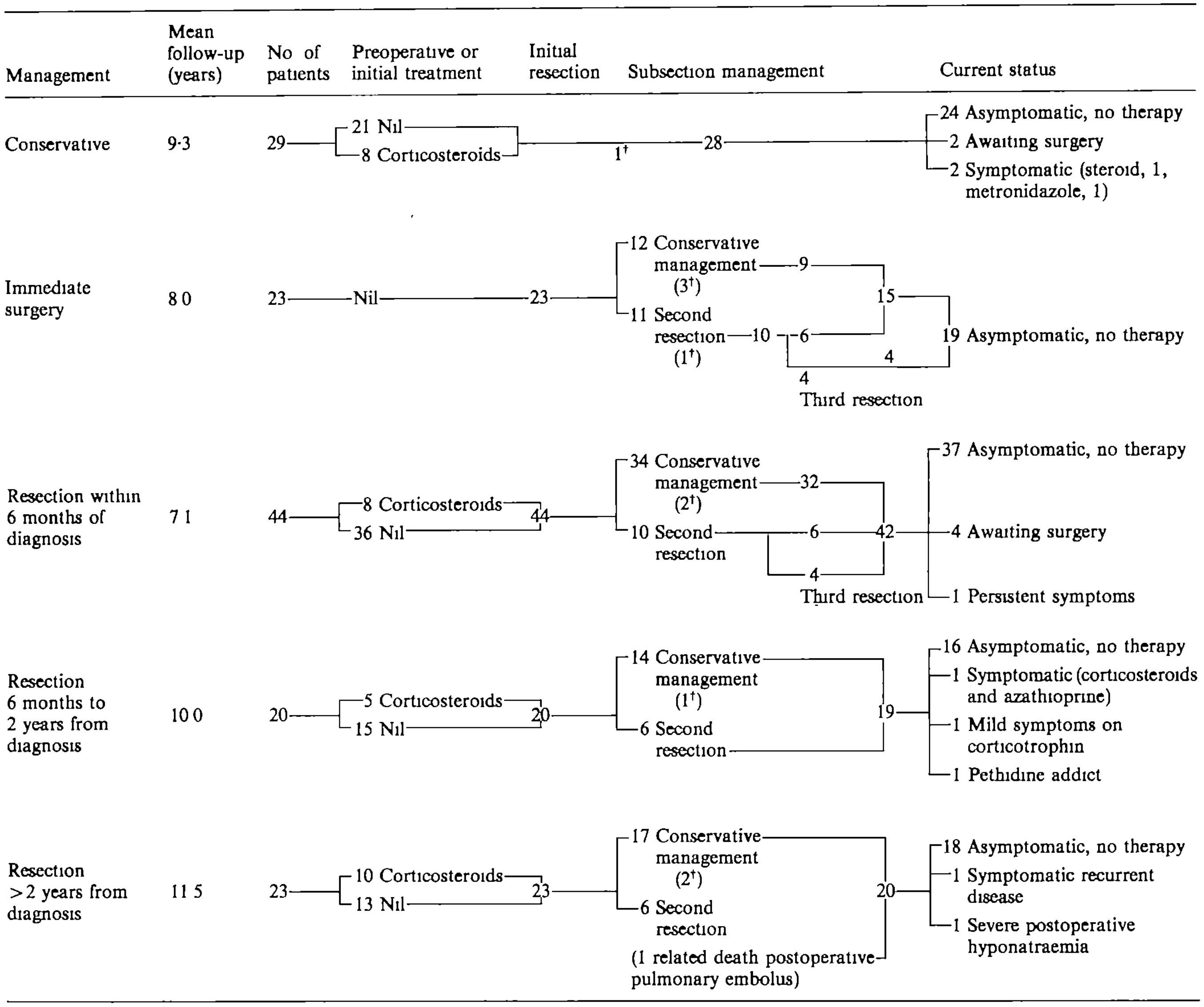
Figure 1 *Outcome of distal ileal Crohn's disease in 139 patients*



Management
Mean follow-up (years)
No of patients
Preoperative or initial treatment
Initial resection
Subsection management
Current status
Conservative
9·3
29
21 Nil
8 Corticosteroids
1†
28
24 Asymptomatic, no therapy
2 Awaiting surgery
2 Symptomatic (steroid, 1, metronidazole, 1)
Immediate surgery
8 0
23
Nil
23
12 Conservative management (3†)
9
11 Second resection (1†)
10
6
15
4
4
Third resection
19 Asymptomatic, no therapy
Resection within 6 months of diagnosis
7 1
44
8 Corticosteroids
36 Nil
44
34 Conservative management (2†)
32
10 Second resection
6
4
Third resection
42
37 Asymptomatic, no therapy
4 Awaiting surgery
1 Persistent symptoms
Resection 6 months to 2 years from diagnosis
10 0
20
5 Corticosteroids
15 Nil
20
14 Conservative management (1†)
6 Second resection
19
16 Asymptomatic, no therapy
1 Symptomatic (corticosteroids and azathioprine)
1 Mild symptoms on corticotrophin
1 Pethidine addict
Resection >2 years from diagnosis
11 5
23
10 Corticosteroids
13 Nil
23
17 Conservative management (2†)
6 Second resection
(1 related death postoperative pulmonary embolus)
20
18 Asymptomatic, no therapy
1 Symptomatic recurrent disease
1 Severe postoperative hyponatraemia

† Unrelated deaths

0–16 years) The interval was similar for the primary and referred patients The diagnosis was delayed in 25 patients by 1–2 years, in 14 by 2–5 years and in 13 by >5 years. The interval could not be determined in five patients. The diagnosis was established by contrast radiology in 95 patients (68 per cent) and at laparotomy for acute abdominal symptoms in 44 (32 per cent)

The commonest symptom at presentation was colicky abdominal pain (108 cases) with one or more additional features including diarrhoea (77 cases), weight loss (52 cases), vomiting (24 cases), anorexia and malaise (23 cases). Twelve patients presented with a mass in the right iliac fossa and nine presented as 'acute appendicitis' Uncommon presentations included growth retardation (2 cases), enterocutaneous fistula (2 cases), and one example each of macrocytic anaemia, depression and unexpected diagnosis at laparotomy for gallbladder disease.

To achieve complete follow-up all patients with Crohn's disease at diagnosis were entered into a computer file recording name, sex, date of birth, date of onset of symptoms and diagnosis, the outcome and late last seen. Additional data extracted from the medical records were added subsequently including the date and nature of any operations, other complications and details of follow-up including recent investigations. All information used in this study was confirmed from the original medical records

Results

The outcome was analysed in five groups of patients. The first group comprised those treated conservatively and the four surgical groups included those undergoing immediate surgery, early surgery (within 6 months of diagnosis), intermediate surgery (6 months to 2 years from diagnosis), or delayed surgery (>2 years from diagnosis) (*Figure 1*).

Conservative management

Twenty-nine patients, mean age at diagnosis 35·7 years (range 14–73 years) were followed for an average of 9·3 years (range 8 5–18 0 years) from diagnosis and experienced a benign course without operation. Throughout the period of review 13 were never admitted to hospital, and of the remaining 16, treated as in-patients, only six had more than one admission. Total duration of hospital stay was <6 weeks for all but one patient.

Twenty-one patients never received specific medication and 18 are now well, including one who was well when lost to follow-up. One died of myocardial infarction; two are having surgical treatment shortly.

Eight patients received short courses of corticosteroids of whom six are now well and not taking specific medication. The seventh has extensive colonic disease and continues on corticosteroids and the eighth has severe perianal disease treated with metronidazole.

Immediate surgery – resection at diagnostic laparotomy

Twenty-three patients, mean age at diagnosis 41·1 years (range

17–93 years), were treated by distal ileal resection with or without resection of the ascending colon at diagnostic laparotomy, and were followed on average for 8 years after operation.

Twelve had no further resections of whom three have since died of unrelated causes. Nine are now fit and asymptomatic although four have radiological changes consistent with recurrent disease.

Eleven patients had a second resection of whom four had a third resection. There was one unrelated death. The ten survivors are all asymptomatic and none has received specific therapy, although two now have radiological evidence of recurrent disease.

All but two of the 23 patients undergoing initial resection were in hospital for <4 weeks. Since resection seven have not needed re-admission, nine have been re-admitted once, four on two occasions, and only three have had more frequent re-admissions.

Resection within 6 months of diagnosis

Forty-four patients underwent resection within 6 months of diagnosis. Eight had been treated with corticosteroid therapy before resection. Only 20 patients were treated as in-patients before surgery, of whom two (who had both been referred to the unit) stayed >4 weeks. At the time of initial resection 35 patients were in hospital for ⩽2 weeks, eight had in-patient stays of 3–8 weeks and only one had a prolonged in-patient stay.

The mean duration of follow-up after resection was 7·1 years (range 8·5–16 years). No further surgical treatment was required by 34 patients, of whom two died of unrelated causes. Of the 32 survivors 28 are well and taking no specific treatment, although six have radiological evidence of recurrent disease Four patients are symptomatic and need further surgery.

Ten patients have had a second resection of whom six have had a third resection. In this group three have had recurrent problems. However, nine of the ten patients are now well.

Resection 6 months to 2 years after diagnosis

Twenty patients were treated by resection 6 months to 2 years after diagnosis, of whom five received corticosteroids before operation. Ten had one preoperative admission, one had two admissions and only one had multiple preoperative admissions. At the time of their first resection the duration of hospital stay was <2 weeks for all but one patient.

After a mean follow-up of 10 years after initial resection, 14 had no further surgery of whom 12 are well and not taking any specific medication. One is symptomatic and taking corticosteroids and azathioprine, and one died of unrelated causes.

Only six patients have had a second resection for recurrent disease of whom four are now well. One is mildly symptomatic and taking corticotrophin. The sixth patient is a pethidine addict.

During follow-up from initial resection six patients have been re-admitted on one or two occasions and only four have been re-admitted more than twice. One has recurrent problems (the pethidine addict).

Resection undertaken >2 years from diagnosis

Surgery was carried out >2 years from diagnosis in 23 patients of whom 16 were referred from other centres. The mean interval from diagnosis to surgery was 6·5 years (range 2·2–15·1 years). Before resection ten had received specific therapy.

Before operation 11 patients had been admitted on one occasion and five more than once. The duration of stay was <4 weeks for all but two patients. At the time of resection all but four patients were admitted for <4 weeks.

After a mean follow-up of 11·5 years after initial resection (range 6–18 years) 17 had no further surgery. Two patients died of unrelated causes. Thirteen are well, one is unwell with symptomatic recurrent disease and one is severely disabled from postoperative hyponatraemia.

During follow-up six patients had further resections of whom five are now well; the sixth patient died of a pulmonary embolus after surgery and an adenocarcinoma was found in the resected specimen. This is the only death related to Crohn's disease in the series.

Current status

Of 139 patients, 11 died; ten of unrelated causes. Of the 128 living patients, 114 are symptom free although 14 have radiological evidence of recurrent disease. Six patients either need or have refused further surgery and could readily be restored to good health. Eight patients are symptomatic: four are taking specific therapy, two are taking symptomatic relief only, one is addicted to pethidine, and one is severely disabled secondary to severe postoperative hyponatraemia

Discussion

A consistent management policy emerged from an earlier study of Crohn's disease of the distal ileum[5] and was used throughout this study. Because the unit acts as a referral centre there is a preponderance of severely ill patients The outcome for the primary and referred groups was similar; there was a higher proportion of referred patients in the delayed surgical group who had often received prolonged specific medical treatment before referral. Once incorporated into the consistent management policy the two groups were indistinguishable.

The delay between the onset of symptoms and diagnosis was 1–2 years in 25 patients, 2–5 years in 14, and >5 years in 13. The delay in diagnosis occurred in both the primary and referred groups. The presenting features were typical, with abdominal pain, diarrhoea, and weight loss, but these features were usually either mild or intermittent, diagnosis being established only when they became persistent. The delay reflects the presence of mild symptoms in an age group when most patients have functional symptoms. Common investigations requested for the investigation of patients with abdominal pain include upper gastrointestinal endoscopy, abdominal ultrasonography and barium enema examination. These are usually all normal in patients with distal ileal Crohn's disease, particularly if during the enema examination barium does not reflux into the distal ileum. Barium follow-through examination should be performed in patients with atypical or persistent abdominal symptoms which remain unexplained, particularly if any laboratory indices are abnormal.

More than a fifth of patients have mild disease with few symptoms even after prolonged follow-up. The good long-term outcome was unrelated to intensive medical therapy and represents the benign end of the spectrum of disease; this proportion might well be higher in an unselected series.

The outcome of surgical treatment has been analysed in four groups and was similar in respect of re-operation rates for recurrent disease, mortality rates and long-term prognosis In particular, delaying surgical intervention did not reduce re-operation rates for recurrent disease. The timing of surgery was determined by the frequency and severity of symptoms, particularly recurrent obstructive symptoms and the development of enterocutaneous fistula or abscess formation.

The number of admissions and duration of hospital stay was used as an index of severity. Hospital admissions were usually infrequent and short; only occasional patients had either prolonged or frequent re-admissions. Among the patients receiving conservative management alone only one had either prolonged admission or frequent re-admissions. The numbers of such patients in the surgically-treated groups were three, one, four and four respectively. Surgical treatment was effective in restoring patients to good health and normal activity. Patients receiving specific medical treatment were often symptomatically better but were rarely completely fit and well.

Only one of the 139 patients died of causes related to their Crohn's disease. The excess mortality rate previously associated with Crohn's disease has now been largely eliminated, apart from an occasional death from digestive tract carcinoma[6]. There were ten unrelated deaths and the pattern of mortality was similar to that experienced in the general population. The long-term outcome for 128 living patients is excellent; 114 are well.

In experienced hands surgical intervention is an effective and rapid method of restoring patients to good health and is usually a good alternative to prolonged medical treatment during which the patient is improved but often remains unwell. Our approach to management has had a successful outcome in nearly all patients. The improvement in mortality rate noted in an earlier study[5] has continued and there has been only one related death in the series between 1970 and 1988. The mortality rate experienced in this hospital series is close to that in the population survey from Copenhagen[7] in which survival with Crohn's disease was no different from that of the general population.

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Case report

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Encysted pneumatocele: a complication of diverticular disease

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We report two unique cases in which an encysted pneumatocele was formed from an acquired pulsion diverticulum of the sigmoid colon.

Case reports

Case 1

A 74-year-old man presented with a painless, resonant, mobile mass in the left iliac fossa which had been noticed for 3 weeks and was visible on an erect plain abdominal radiograph. Barium studies confirmed the presence of a gas-filled cavity arising from the sigmoid colon; this could not be outlined by barium but expanded during insufflation of air. Elective sigmoid colectomy was performed incorporating a 6 cm diameter cyst arising from the antimesenteric border of the colon. The patient made an uncomplicated recovery. Histological examination confirmed the presence of diverticular disease. Several of the diverticula were heavily inflamed with focal abscess formation. Sections of the cyst showed a thick fibrous wall lined by granulation tissue with foreign body giant cells reacting to faecal material. There was no evidence of an epithelial lining and smooth muscle was not identified within the wall of the cyst.

Case 2

A 63-year-old man was referred with a painless mass in the right iliac fossa which had been present for 3 weeks and was associated with anorexia, weight loss and abdominal pain. Plain abdominal radiographs confirmed a gas-filled cavity. Barium studies demonstrated a gas-filled cavity arising from the sigmoid colon which expanded with insufflated air but did not permit the entry of barium (*Figure 1*). At elective laparotomy a cystic mass arising from a single diverticulum was resected and the colonic defect oversewn. He then developed a faecal fistula and required sigmoid colectomy from which he made a good recovery. Histopathological examination revealed a 6·5 cm diameter cyst arising from a single diverticulum. Granulation tissue lined a thick fibrous tissue wall which contained a chronic inflammatory infiltrate.

Discussion

Our cases present a number of interesting features. In both, barium would not enter into the cyst but increasing the intraluminal pressure at insufflation allowed air to enter and expand the cyst. This may be the mechanism that allowed continued expansion of the cyst wall *in vivo*. It is unusual for inflammatory lesions to be asymptomatic, as in the first case described, and well defined, mobile cystic masses are rare findings in the male abdominal cavity. Contrast radiology readily demonstrated the site and nature of the lesion and laparotomy confirmed the benign nature of the mass.

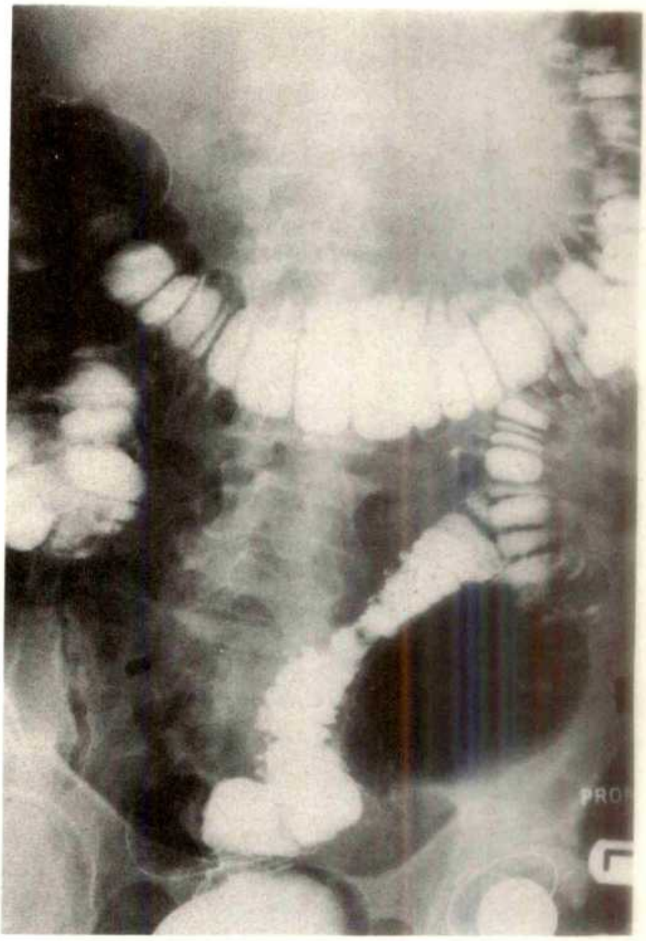

Figure 1 *Barium enema radiograph of case 1 showing air-filled cyst arising from sigmoid colon*

The differential diagnosis is that of 'mesenteric cysts' which are usually incidental findings but may be large enough to produce symptoms. This term includes chylous cysts which arise from lymph vessels and have an endothelial lining; such cysts may become large and multilocular with smooth muscle in their walls when they are regarded as cystic lymphangiomas. Bowel duplications are cysts lined by intestinal mucosa which have a smooth muscle layer and connect with the bowel proper; these duplications are usually diagnosed before 6 months of age. Other cystic lesions include benign cystic mesothelioma lined by mesothelium and mesenteric cysts lined by muellerian epithelium.

In our cases no epithelial lining was identified and the wall of the cyst consisted of fibrous tissue only. Formal colonic resection should have been the treatment of choice to prevent complications and to reduce the risk of faecal fistula formation from the abnormal colonic wall following simple excision of the cyst and direct closure of the defect.

Acknowledgements

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Devine exclusion for unresectable carcinoma of the stomach

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Between July 1986 and July 1988, Devine exclusion was performed in 20 patients with unresectable carcinoma of the gastric antrum. All 20 patients presented with repeated vomiting. On endoscopy, 16 patients had complete gastric outlet obstruction while the remainder manifested significant gastric outlet stenosis. There was no hospital mortality. All except two patients could take an oral diet after surgery until their demise. Devine exclusion is safe and effective in relieving gastric outlet obstruction and is not associated with prolonged delay in return of gastric emptying.

In most centres, the majority of patients with carcinoma of the stomach present with advanced disease. In Birmingham, 75 per cent of 12 737 patients presenting with gastric cancer were not resectable[1]. In patients with unresectable carcinoma causing gastric outlet obstruction, gastroenterostomy has been the palliative operation of choice but has a high incidence of delayed gastric emptying. We report our experience in 20 consecutive patients with unresectable antral carcinoma treated by Devine antral exclusion.

Patients and methods

Between July 1986 and July 1988, 129 patients underwent surgery for carcinoma of the stomach. Ninety-four (72·9 per cent) patients had either a curative or a palliative resection while in 15 patients (11·6 per cent) the disease was so extensive that any surgical procedure was not considered of benefit.

The remaining 20 (15·5 per cent) patients with unresectable antral carcinoma had a Devine antral exclusion. There were eight men and 12 women with an age range of 56–78 years (mean age 71 years). All presented with recurrent vomiting. On fibreoptic gastroscopy, the endoscope could not be passed into the duodenum in 16 patients. Six patients also had evidence of gastrointestinal haemorrhage. At laparotomy all 20 had locally advanced tumour of the antrum infiltrating the head of the pancreas or the porta hepatis. Five patients had liver metastases and four had peritoneal metastases.

After it was confirmed that the primary antral tumour was unresectable, the proximal stomach was mobilized and transected just proximal to the tumour. The distal stomach bearing the tumour was closed with a TA90 stapling gun (US Surgical Corporation, East Norwalk, Connecticut, USA) in 16 patients or by suturing in four patients. A jejunal loop was then brought up to the proximal stomach and an antecolic isoperistaltic gastroenterostomy was fashioned (*Figure 1*). Six of these were created with the GIA stapling gun (US Surgical Corporation) and 14 by hand suturing.

Results

There was no hospital mortality. All patients resumed oral diet within 3–8 days (median 5 days). Postoperative hospital stay ranged from 5 to 13 days (median 7 days). All patients were followed up monthly. Nineteen patients were dead at the time of analysis. The survival period ranged from 1·5 to 16 months (median 3 months) after operation. Two patients developed recurrent obstruction at 4 and 5 months respectively due to extrinsic tumour compression rather than anastomotic recurrence. Seventeen patients were able to eat until their demise and the sole surviving patient was still taking a normal diet 3 months after operation.

Complications developed in four patients. One patient had a wound dehiscence, another had a wound infection, one developed a chest infection and one other patient complained of bilious vomiting.

Discussion

For patients with incurable gastric cancer, resection still offers the best symptomatic palliation[2] if the primary tumour can be removed safely. Extensive fixation to the retroperitoneal structures such as the pancreas and the porta hepatis make resection hazardous. For these patients bypass surgery is worthwhile to relieve recurrent vomiting due to gastric outlet obstruction. Gastroenterostomy is the most commonly advocated bypass procedure for obstructed carcinoma of the gastric antrum[3]. In patients who had gastroenterostomy for malignant gastric outlet obstruction, 10 per cent have significant delay in the return of gastric emptying[4]. This is partly because the anastomosis cannot be created in the most dependent part of the stomach and partly due to early submucosal tumour encroachment on the anastomosis.

In 1925, Devine[5] described antral exclusion in the management of difficult duodenal ulcers. The operation was quickly abandoned because of an unacceptably high incidence of anastomotic ulcers, but Maingot[6] adapted the procedure for the treatment of unresectable antral tumour. The advantage of the Devine procedure is that an end-to-side anastomosis is performed in a dependent position away from the primary tumour.

In our hands, Devine exclusion has proved to be a safe and reliable method of relieving distressing vomiting in patients with advanced, unresectable carcinoma of the stomach. In contrast to Devine's original series of patients with duodenal ulcers,

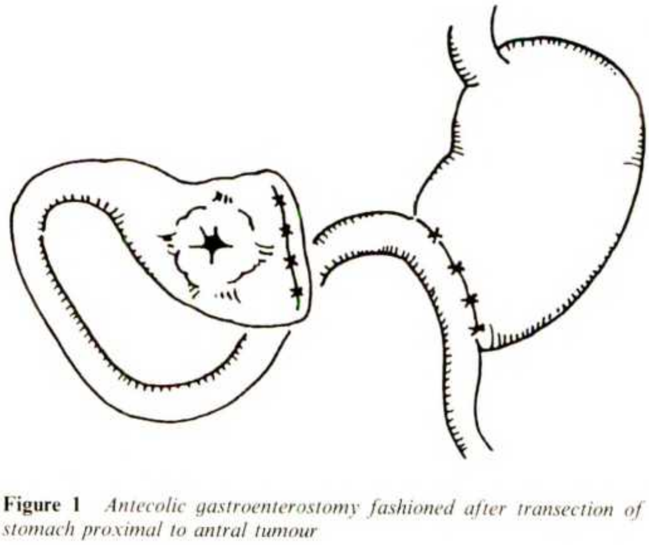

Figure 1 *Antecolic gastroenterostomy fashioned after transection of stomach proximal to antral tumour*

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anastomotic ulceration was not encountered in our patients. Diversion of food and acid from the tumour surface in Devine exclusion might also lessen tumour haemorrhage. Although subclinical bleeding is difficult to document, the six patients who had preoperative gastrointestinal haemorrhage required no further blood transfusion after operation until their death.

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Short note

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Optimum duration of surgical scrub-time

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The concept of a 'good' surgical scrub has undergone much refinement. Price has shown that scrubbing with ordinary soap and water for 5 min reduces the mean viable bacterial count of the hands by only 50 per cent[1]. Prolonged scrubbing with soap and running water has thus been gradually replaced with detergent preparations and running water. With more effective detergents, there is an increasing tendency to shorten the scrub-time.

The purpose of this study is to compare the effectiveness of a 2-min, a 4-min and a 6-min surgical scrub on the hand bacterial colony count using Hibiscrub® (I.C.I. Pharmaceuticals, Macclesfield, UK; 4 per cent chlorhexidine solution).

Materials and methods

The hand bacterial colony counts of ten surgical staff members about to undertake clean abdominal operations (as defined by Cruse[2] and Pollock[3]), but who had not scrubbed within the previous 24 h, were studied. Each participant engaged successively in a 2-min, a 4-min and a 6-min scrub, on separate days, as follows.

The hands were initially washed in unmedicated (buttermilk) soap and running water for 30 s and dried with a sterile towel. Using the modified Peterson glove-rinse technique[4], both hands were then sampled for determination of 'prescrub counts'. Hibiscrub was next applied in a systematic fashion for 2, 4 or 6 min One litre of sterile water was used to rinse the residue from the hands which were again dried with a sterile towel Samples were then taken for 'postscrub counts' Gloves were removed after 1 h and further samples were taken to estimate the '1-h postscrub counts'.

All samples were immediately plated and then incubated at 37°C for 48 h. Bacterial colony counts were measured and were expressed as $\log_{10}$/ml.

Statistical analysis was done using Student's *t* test.

Results

Both hands in ten subjects were studied for each of the three time periods. The results are tabulated in *Table 1*

The reduction in hand bacterial colony count was statistically significant in all three groups at 1 h. A greater reduction was seen in both the postscrub and 1-h postscrub counts in the 4-min and 6-min groups when compared with the 2-min group, this did not reach statistical significance.

There were no postoperative wound infections. No antibiotic cover was used.

Discussion

The purpose of a surgical scrub is the removal of dirt and grease, as well as both transient and resident flora[5]. The use of an antiseptic agent is more effective than bar soap for this purpose[6]. Using the USA Food and Drug Administration's methodology, Peterson has shown that 4 per cent chlorhexidine gluconate (Hibiscrub) produces the best immediate and persistent reductions in normal hand flora when compared with 0·75 per cent povidone–iodine (Betadine®, Napp Laboratories Ltd, Cambridge, UK) and 3 per cent hexachlorophene (pHisoHex®, Winthrop, New York, USA). In order to minimize any deficiency that a shorter scrub-time might have, we decided to use Hibiscrub as the sole antiseptic agent. We also standardized the source and amount of the water used to rinse off the disinfectant.

A reduction in the postscrub counts was achieved in all three groups. Although this difference did not reach significance in the immediate postscrub counts, the antiseptic action persisted and resulted in a further progressive reduction which did reach statistical significance in the 1-h postscrub counts The actual

Table 1 *Hand bacterial colony counts following surgical scrubbing with 4 per cent chlorhexidine solution (Hibiscrub) for 2-min, 4-min and 6-min durations*

	Colony counts ($\log_{10}$/ml)		
Scrub-time	Prescrub	Immediate postscrub	1-h postscrub
2-min	4·9(0·5)	4·1(0·6) (16%)*	2·6(0·7) (47%)†
4-min	4·4(0·8)	3·5(0·9) (20%)*	2·0(0·9) (55%)†
6-min	4·5(0·9)	3·1(0·7) (31%)*	1·9(0·5) (58%)†

Values are mean(s.e.m.); percentage figures give reduction in hand bacterial colony counts compared with prescrub counts, * no significant difference compared with prescrub count; † $P < 0.01$ compared with prescrub count

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reduction required, however, has never been determined[8]. The fact that none of the three different scrub-times and resultant counts were associated with any case of wound infection suggests that the count reductions achieved were adequate for the clinical setting.

The advantages of a shorter scrub-time were clearly outlined by Galle *et al.*[9]. They included a reduction in skin trauma and dermatitis, a saving in water consumption (it is estimated that 50 gallons of water are used in a single 10-min scrub), and a saving in actual theatre time. Other studies have also shown shorter scrub-times to be as effective as more prolonged times[9–11].

In conclusion, all scrub-times proved to be perfectly adequate in the clinical setting, and scrubbing for longer than 2 min does not confer advantage in terms of reducing hand bacterial colony counts. We recommend a 4-min scrub for the first case on the operating list, and a 2-min scrub for remaining procedures, taking into account the persistent and cumulative antiseptic effect of 4 per cent chlorhexidine (Hibiscrub). This is a safe and cost-effective routine which should appeal to most surgeons.

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Perineal excision of the rectum for prolapse in the elderly

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A perineal operation is described for the treatment of rectal prolapse. The surgery improves functional outcome by correcting the anatomical anomalies associated with the condition. In 17 elderly women, there was one perioperative death and one recurrence. At a median follow-up of 24 months, 13 patients were able to control solid stool and three were profoundly incontinent. The operation may be an alternative to the more invasive abdominal procedures for the treatment of the majority of patients with prolapse.

Complete rectal prolapse is a distressing condition of elderly women which may necessitate institutional care. It is important, therefore, to consider surgical correction even in frail patients and, because abdominal rectopexy is invasive and potentially hazardous, several perineal approaches have been devised[1–5] but none is widely accepted.

The anatomical anomalies associated with rectal prolapse are a patulous anus, diastasis of the levator ani muscle, loss of the sacral attachment of the rectum, and a deep peritoneal reflection[6]. A technique is described for perineal excision of the rectum, which by correcting these anomalies aims to improve the functional outcome after perineal surgery for prolapse.

Patients and methods

The operation was performed in 17 women (median age 82 years, range 60–92 years). Ten had been refused abdominal rectopexy by other surgeons and the remaining seven had cardiorespiratory disease which made an abdominal procedure undesirable. Seven patients were severely confused before surgery

Operative procedure

The bowel was prepared with a disposable enema. The operation was performed under general anaesthesia in 15 patients and with regional anaesthesia (caudal block) in two. After insertion of a urinary catheter all patients were placed in the prone position and given antibiotic prophylaxis.

Operative technique

The operation aims to correct all the anomalies associated with rectal prolapse '(*Figure 1*). The prolapse is reduced and an Eisenhammer retractor is placed in the anal canal A 1:200 000 solution of adrenaline is infiltrated submucosally to approximately 3 cm above the dentate line. Using the dissection diathermy the mucosa is stripped as a cuff from the dentate line to the level of the puborectalis, preserving the internal sphincter (*Figure 2*, dissection 1).

The redundant rectum is then drawn from the anal canal using sponge-holding forceps, and the full thickness of the rectal wall immediately above the puborectalis is divided using diathermy and directing the incision towards the sacrum (*Figure 2*, dissection 2). The tissue at this point is thin and the posterior dissection is safe due to the laxity of the attachment of the rectum to the sacrum and the bloodless plane. The extrarectal space is entered immediately above the levator and the dissection is continued forward on both sides, dividing the bowel wall.

Anteriorly, care is taken to identify the rectovaginal septum above the sphincter, since the vagina may be a thin structure in the elderly (*Figure 2*, dissection 3) The dissection proceeds upwards between the rectum and vagina in a bloodless plane until the rectum is freed and may be drawn through the sphincter muscles (*Figure 3*). The lateral ligaments are not divided and the rectum is allowed to protrude until taut The protruding rectum (which also contains a deep peritoneal reflection anteriorly) is retracted forward to allow access to the puborectalis muscles posteriorly, which are plicated using interrupted sutures (*Figure 4*). The sphincter is plicated both anteriorly and posteriorly until the rectum is held snugly, adopting its pelvic position following the curvature of the sacrum, thereby reconstructing the anorectal angle (*Figure 5a* and *b*).

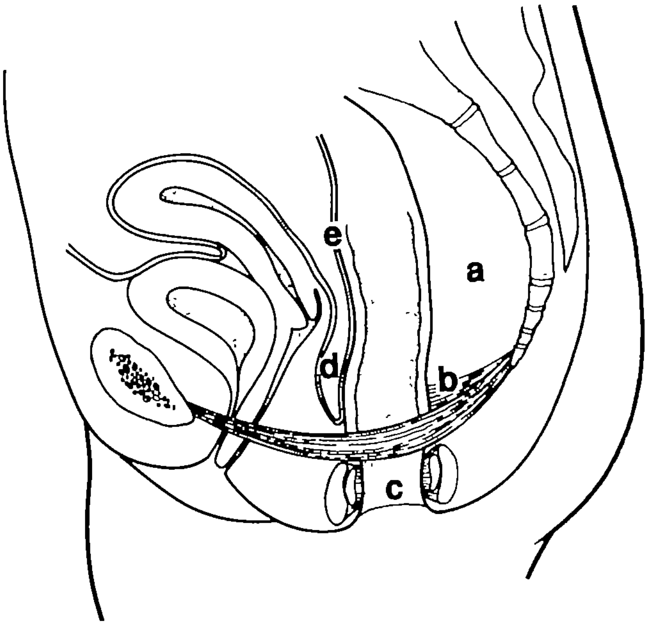

Figure 1 *Anatomical anomalies associated with rectal prolapse* (**a** *loss of sacral attachment of the rectum,* **b** *diastasis of the levator ani muscles,* **c** *patulous anus,* **d** *deep peritoneal reflection;* **e** *redundant sigmoid colon*)

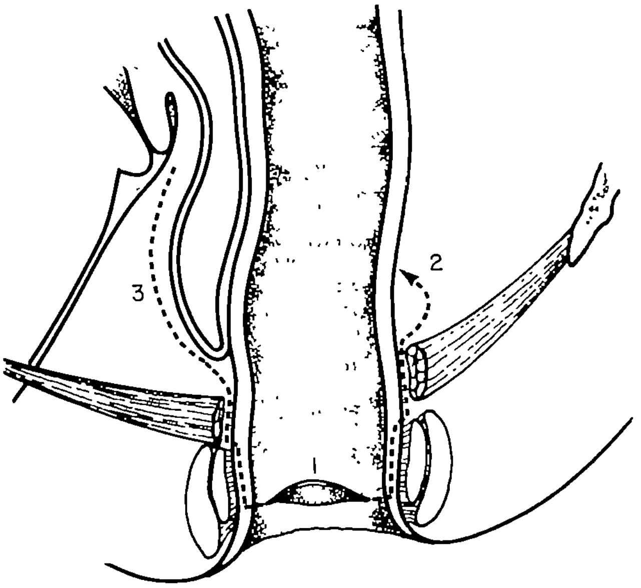

Figure 2 *Planes of dissection. 1, Circumferential mucosal stripping to level of puborectalis, 2, posterior full-thickness division of bowel wall, 3, bloodless plane between rectum and vagina above the sphincter*

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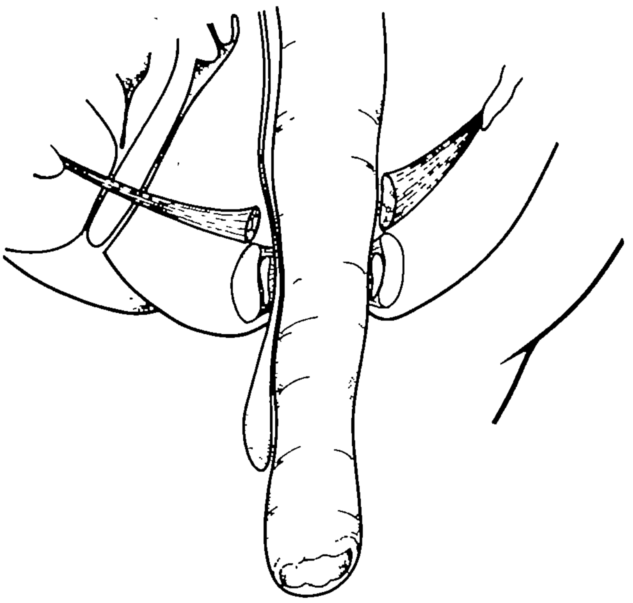

Figure 3 *Mobilized rectum with deep peritoneal reflection is pulled through the anus until taut*

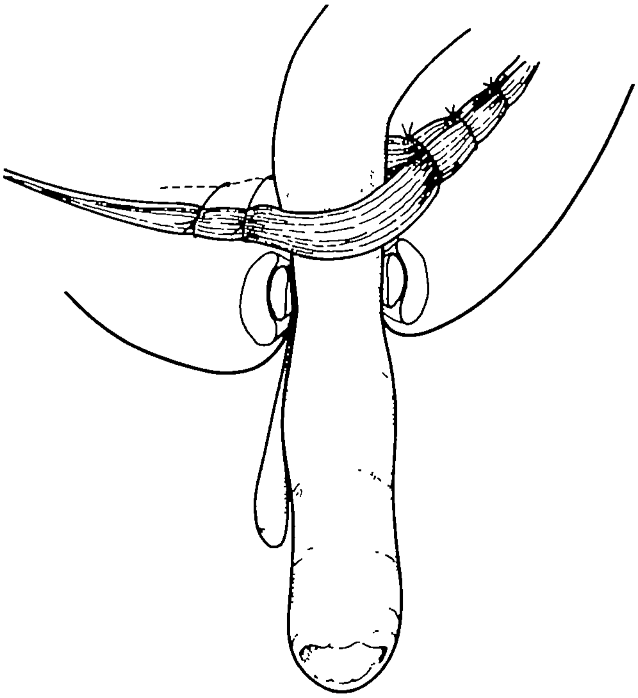

Figure 4 *Plication of the levator anteriorly and posteriorly is undertaken using protruding rectum as a retractor to facilitate access*

The freed rectum which protrudes at the anus is then opened along its length and sutured to the dentate line using 2.0 Vicryl® (Ethicon Ltd, Edinburgh, UK), taking full bites of the internal sphincter (*Figure 5c*). The rectum is opened circumferentially, progressively securing the full thickness of the rectum to the dentate line by placing sutures on alternate sides. At the anterior aspect of the rectum the protruding peritoneal cavity is encountered as a hernial sac (*Figure 5d*); a simple herniotomy is performed and the anastomosis is completed.

No dressings are used. A caudal block is inserted and free fluids are given on the first day after operation. Diets and aperients are commenced on day 3.

Continence was assessed at 6 months by interview with patients and/or their attendants and was classified as (a) normal; (b) moderate (continent to solid stool but having minor leakage controlled by wearing a pad), and (c) incontinent (unable to control formed stool).

Results

One patient died from myocardial infarction in the postoperative period (in-hospital mortality rate of 6 per cent). The median duration of surgery was 60 min (range 35–75 min), and the median length of rectum resected was 14 cm (range 3–36 cm)

Three patients developed complications during the immediate postoperative period. These included a cardiovascular accident, cardiac arrhythmia and a rectovaginal fistula. The latter was closed successfully by simple suture.

The median follow-up for the 16 patients surviving surgery was 24 months (range 10–40 months). One recurrent prolapse occurred during the immediate postoperative period, and at 6 months eight patients were completely continent; five had slight leakage and needed to wear a pad, but this did not interfere with their daily activity. Three patients (including the patient who had an immediate recurrence) were severely incontinent.

Discussion

The ideal operation for rectal prolapse should be minimally invasive, correct all the anatomical abnormalities, and restore continence with no morbidity. To achieve these goals, several perineal approaches have been described. The simplest, attributed to Thiersch, involves suture of the patulous anus, correcting only one anatomical anomaly associated with rectal prolapse[7]. The results, however, are poor, with recurrence rates as high as 68 per cent[8,9].

A more complex procedure described by Delorme in 1900[12] involves stripping of the rectal mucosa with plication of the denuded muscle. This procedure may be considered a dynamic Thiersch operation, correcting the anomaly of the patulous anus by plicating the muscle of the bowel wall and reducing the length of the redundant rectum (correcting two of the anatomical abnormalities). Although the results are superior to the Thiersch procedure, reported recurrence rates range from 7 to 32 per cent[3,5,11], with little information regarding subsequent continence.

Altemeier described a more complex procedure of perineal rectosigmoidectomy with a coloanal anastomosis. This operation has the advantage that the redundant bowel is removed and there is opportunity for plication of the pelvic floor with excision of the peritoneal hernia. Altemeier reported a recurrence rate of only 3 per cent but others have found the operation disappointing with very high recurrence rates[12]. This may occur because a pull-through technique is used, with division of the rectum and the anastomosis performed outside the anal canal. Inevitably there is a small residual prolapse when the anastomosis is returned to the anal canal. Despite this limitation the technique has been simplified by using the circular stapling instruments, with satisfactory results[13].

The operation described in the present paper combines features of both the Delorme and the Altemeier procedure, and

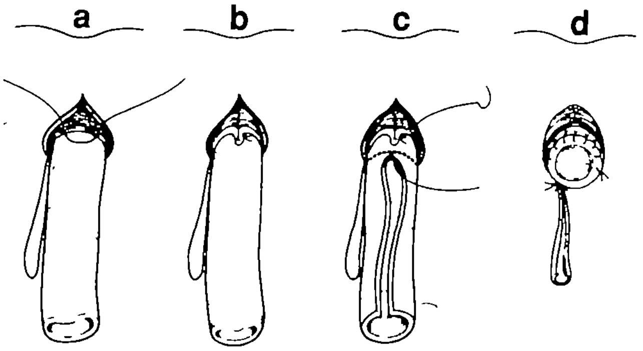

Figure 5 **a** *and* **b** *Sphincter is plicated;* **c** *redundant rectum is opened along its length and secured to the sphincter,* **d** *deep peritoneal reflection is encountered as a hernial sac anteriorly, and a herniotomy is performed*

attempts to correct all the anatomical abnormalities associated with prolapse. The technique is no more difficult to perform than either of the individual operations and results in minimal morbidity The advantage over the Delorme procedure is that it allows excision of the deep peritoneal reflection, amputation of the redundant bowel, recreation of the anorectal angle and plication of the pelvic floor. Unlike the Altemeier procedure, the anastomosis is performed at the dentate line avoiding the dangers of an anastomosis in the pelvis without leaving a small residual prolapse.

The present procedure should have the advantages of the Delorme and Altemeier without the disadvantages. The functional results obtained in the present series would support this. The major disadvantage of perineal operations in the past has been poor continence and a high incidence of recurrent prolapse In the present study most patients had an acceptable degree of continence and it is of interest that no patient in the present series complained of constipation. This compares well with recent results of rectopexy, in which up to 36 per cent of patients were incontinent and a further 50 per cent suffered from severe constipation which was difficult to treat[14–16]. One patient in the present study had a recurrent prolapse in the immediate postoperative period, presumably due to technical failure, but to date there are no late recurrences at up to 2 years.

The present operation was primarily designed to improve the functional results of perineal operations for rectal prolapse in the elderly. As these results compare with those of previous reports of rectopexy, and the procedure avoids laparotomy and does not preclude a subsequent rectopexy, perineal excision is now offered as the first surgical option to the majority of patients with prolapse.

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Anismus in patients with normal and slow transit constipation

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This study examined differences in anorectal function, with particular reference to anismus, which might explain why some patients with intractable constipation have slow and others have normal whole gut transit times. Twenty-four patients were studied; 13 with slow transit (all female, median age 32 years, range 16–52 years) and 11 with normal transit (eight women, three men, median age 37 years, range 21–60 years). Videoproctography with synchronous sphincteric electromyography and anorectal manometry was performed. There were no differences between the two groups, suggesting that slow transit constipation is not secondary to any abnormality in anorectal function and may therefore be a primary disorder of colonic motility. There was no correlation between electromyographic evidence of anismus (pelvic floor contraction on defaecation) and the ability of the patient to evacute the rectum or symptoms of obstructed defaecation. Electromyography findings alone can be misleading and should be related to proctographic evidence of incomplete rectal evacuation before functional anismus can be said to be present.

Current knowledge of the pathophysiology of intractable idiopathic constipation is limited and results of treatment are at best unpredictable[1]. Whole gut transit time divides patients into those with normal and slow transit[2] but other abnormalities exist in these groups, for example anismus (pelvic floor contraction on attempted defaecation). It is tempting to ascribe the constipation of patients with normal transit to pelvic floor dysfunction. The aim of this study was to determine whether there were differences in physiological and radiological parameters between patients with normal and slow transit and whether electromyographic evidence of anismus correlated with radiographic evidence of pelvic outlet obstruction and patient symptoms.

Patients and methods

Patient groups

Twenty-four patients presenting with constipation were studied. They either had fewer than three bowel actions per week and/or they had severe difficulty with evacuation of rectal contents characterized by frequent though ineffective attempts at defaecation with marked straining and self-digitation. They were divided into two groups based on the results of whole gut transit time using intestinal radio-opaque markers[2]. Eleven patients (three men; eight women; median age 37 years, range 21–60 years) had transit times within the normal range and 13 female patients (median age 32 years, range 16–52 years) had slow transit, 20 per cent or more of the markers being retained at 5 days after ingestion.

Study design

All patients were initially seen in out-patients; they underwent clinical examination and sigmoidoscopy, and were referred for further investigations. Ethical permission for this study was obtained from the Bristol and Western Health Authority, and each patient gave their informed consent

Videoproctography with additional manometry and electromyography

The method has been described in detail previously[3] and aims to obtain videographic pictures during attempted defaecation with synchronous manometric information from the anorectum and electromyographic data from the external anal sphincter and puborectalis muscles. Information was passed to three control units allowing the manometric and electromyographic data to be superimposed on the videographic picture of the anorectum (type 31C40, 25B11 and 25B05, Dantec Electronics, Bristol, UK).

Radiology Dilute barium sulphate was infused into the rectum until the patient reported the feeling of rectal fullness and the desire to defaecate. The anorectum was visualized using a 100 mm camera (Sircam 106, Siemens, Elema, Sweden), 0 6 mm focus at 125 kV from a 100 mA generator. The image was displayed on an image intensifier and stored on a Sony Umatic (Sony Corp Incorporated, Tokyo, Japan) tape recorder.

Manometry. Midanal canal and rectal pressures were recorded by a Gaeltec microtransducer catheter (Gaeltec Ltd, Isle of Skye, UK). The output from these microtransducers was amplified and a permanent record was obtained on a chart recorder (type 21C15 amplifier and system 2100 pen recorder, Dantec Electronics)

Electromyography. Using suitable local anaesthesia, two Teflon® (E.I. du Pont, Wilmington, Delaware, USA) coated wires with their tips bared were inserted into the external anal sphincter and puborectalis muscles using a 19 Fr needle which was then withdrawn. The wires were 0 13 mm in diameter and once in place they could not be felt by the patient The output from these electrodes was related to a ground electrode on the patient's back and amplified (type 21C01, Dantec Electronics), and a permanent record was obtained on the chart recorder.

The following details were noted from the video and chart recordings. rectal and sphincter pressures at rest and during defaecation; maximum percentage change in external sphincter or puborectalis electromyographic activity during voluntary contraction of the sphincter and defaecation; anorectal angle at rest in the left lateral position and sitting; and, during defaecation, successful evacuation of the barium and the incidence of rectal intussusception The majority of the barium was evacuated in patients with 'good' emptying while 'poor' emptying meant that only a small amount was passed.

Statistical analysis

All data groups are described as medians with the range in parentheses. The Mann–Whitney U test was used to assess the significance of the differences between the two groups unless otherwise indicated The Spearman rank correlation coefficient was used to determine correlation between various parameters.

Results

Symptomatology

Two of thirteen (15 per cent) patients with slow transit had a normal call to stool compared with eight of 11 (73 per cent) of those with normal transit ($P<0.02$, χ^2 test with Yates'

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Table 1 *Results of videoproctography with additional sphincter manometry and electromyography*

	Normal transit ($n=11$)	Slow transit ($n=13$)
Rectal pressure (cmH_2O)		
Rest	21 (10–50)	20 (5–45)
Defaecation	100 (20–140)	120 (75–150)
Sphincter pressure (cmH_2O)		
Rest	80 (60–175)	100 (40–150)
Defaecation	135 (50–175)	135 (85–250)
Maximum electromyographic change (%)		
Squeeze	400 (0–1000)	700 (300–1000)
Defaecation	100 (−100 to 800)	400 (−400 to 1000)
Anorectal angle		
Rest	110 (95–125)	120 (95–130)
Defaecation	110 (100–140)	125 (95–145)

Values are medians with ranges in parentheses

Table 2 *Results of electromyography, anorectal angles and rectal emptying*

Patient no.	Percentage change in electromyography	Anorectal angle (°)		Rectal emptying
		Rest	Defaecation	
Normal transit				
1	+800	95	100	Good
2	+100	105	105	Good
3	+300	125	125	None
4	0	125	125	None
5	+550	110	110	Poor
6	+300	125	125	None
7	0	120	100	Poor
8	0	120	140	Poor
9	−100	95	120	Good
10	+700	95	105	Good
11	0	100	105	Good
Slow transit				
12	+400	120	130	None
13	0	120	120	None
14	+700	130	120	Poor
15	+600	125	145	None
16	+400	100	130	Good
17	0	125	125	None
18	+900	130	130	Good
19	+400	120	125	Good
20	+400	115	115	Poor
21	−400	120	140	None
22	0	95	95	Good
23	+1000	100	105	Poor
24	+1000	110	115	Good

correction). There was no significant difference between the two groups in the duration of symptoms (slow transit, median 2 years, range from 6 months to 30 years; normal transit, median 4 years, range from 6 months to 30 years). Both groups frequently complained of incomplete evacuation after defaecation and straining at stool. Five patients with slow transit had had a previous hysterectomy as had three of those with normal transit (no significant difference).

Videoproctography with manometry and electromyography

There was no statistical difference between the two patient groups for any of the parameters measured. In both groups there was an increase in the electromyographic activity of the pelvic floor on attempted defaecation, with a tendency for this to be more marked in those with slow transit (*Tables 1* and *2*).

Pelvic outlet obstruction was defined as a failure to open the anorectal angle with poor or no emptying of rectal contents on proctography. There was no correlation between electromyographic evidence of anismus (i.e. increased activity on straining) and proctographic evidence of pelvic outlet obstruction (*Table 2*). Three patients with normal transit and four with slow transit were able to evacuate well despite markedly increased electromyographic activity (*Figure 1*). Others who did not show recruitment of the pelvic musculature were unable to evacuate. There was no correlation between patients' symptoms and electromyographic changes.

Discussion

In a minority of patients with constipation the problem is severe and resistant to conventional treatment. For example a high-fibre diet will often exacerbate symptoms. The patients are often young or middle-aged women who can be divided into two groups depending on the result of whole gut transit studies.

Slow transit constipation (as defined above) has been associated with a number of other abnormalities, gynaecological[4,5], autonomic[6] and psychiatric[7], and there is an association with previous abdominal surgery, particularly hysterectomy[1,5]. This group may have concomitant urinary abnormalities with impaired bladder sensation and inappropriate sphincter activity on voiding.

It has been suggested that outlet obstruction may be due to inappropriate pelvic floor contraction and this may lead to slow transit constipation[8]. These results do not support this hypothesis as both patient groups exhibited electromyographic anismus. These data suggest that a primary abnormality of gut motility is the cause of slow intestinal transit.

The presence of anismus detected by electromyography in this study did not correlate with other tests of defaecatory function, and the definition must be re-examined. If anismus represents outlet obstruction then increased somatic sphincter activity should be associated with a higher anal canal pressure, a more acute anorectal angle, and subsequent difficulty in evacuation.

Shouler and Keighley found impaired rectal sensation, 'reduction' of the anorectal angle, and failure to expel a rectal balloon to be associated with recruitment of puborectalis electrical activity[9]. Bannister *et al.* demonstrated increased

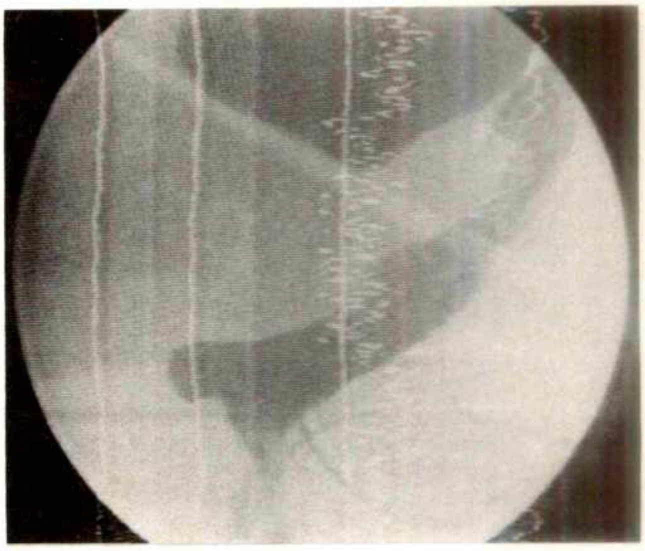

Figure 1 *Lateral radiograph taken during rectal evacuation in a patient with slow transit (anterior is to the left of the figure). This patient was able to empty the rectum and open the anorectal angle despite contracting the pelvic floor musculature as shown by the increased activity of the electromyography channels. The electromyographic activity appears to be unrelated to the patient's ability to evacuate. Channels from left to right: rectal pressure, anal canal pressure, puborectalis electromyographic activity and external sphincter electromyographic activity*

external sphincter activity during straining in 50 per cent of patients with constipation, with reduced rectal sensation and desire to defaecate[10]. This loss of rectal sensation has been noted in children with constipation[11], and is more marked in those with slow transit constipation[12]. Read *et al.* reported normal rectal sensation to balloon distension in a group of young women with slow transit, but increased volumes were required to invoke the desire to defaecate[13].

Kuijpers *et al.* suggested that outlet obstruction leads to retrograde colonic filling and to slow transit constipation[8] and correlated electromyographic recruitment of pelvic floor activity with the failure of the anorectal angle to open[14].

In this study no consistent correlation between electromyographic activity on defaecation with rectal emptying, changes in the anorectal angle, or obstructive symptoms was demonstrated. To define anismus, therefore, the electromyographic changes should be associated with proctographic evidence of failure to evacuate rectal contents on attempted defaecation. Three of the five patients with normal transit and three of four patients with slow transit who emptied their rectum well did so despite electromyographic recruitment. It is inappropriate to classify them as having pelvic outlet obstruction solely on the basis of electromyographic changes. Similarly, half of those with normal transit and over a third of those with slow transit have poor emptying and obstructive symptoms and yet have no evidence of electromyographic recruitment.

Every effort was made to make the investigations as comfortable as possible but the conditions can hardly be described as 'physiological' and these results may not reflect the normal pattern of events for each individual. Greater emphasis should be placed on the proctographic findings of incomplete rectal evacuation when attempting to define patients with anismus.

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Relationship between outlet obstruction constipation and obstructed urinary flow

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Ten women with symptoms and radiological features of outlet obstruction constipation underwent urodynamic bladder studies. The results were compared with ten age- and sex-matched controls. The mean(s.e.m.) peak flow rate for patients was 19·4(6·4) ml/s compared with 32·1(7·2) ml/s for controls ($P<0{\cdot}05$). *The mean(s.e.m.) voiding time for patients was 62·9(23·7) s against a corresponding value of 15·6(6) for controls* ($P<0{\cdot}05$). *The mean(s.e.m.) bladder volume in patients was 482(80) ml compared with a control value of 254(112) ml* ($P<0{\cdot}03$). *The mean residual volume was raised in patients at 45 ml (range 10–150 ml). The mean(s.e.m.) detrusor pressure during the voiding phase was 53·3(12)* cmH_2O. *These results demonstrate that patients with outlet obstruction constipation have a generalized pelvic floor disorder resulting in obstructed urinary flow.*

Outlet obstruction constipation or obstructed defaecation is an increasingly recognized clinical entity comprising symptoms of straining at stool, a sensation of incomplete emptying and tenesmus[1]. The patients, who are invariably female, may attribute the onset of their symptoms to childbirth or previous pelvic surgery[2]. While normal defaecation involves opening of the anorectal angle with relaxation of the puborectalis muscle[3], these patients contract puborectalis on straining at stool (puborectalis paradox)[4,5] and fail to open the anorectal angle

We postulated that if abnormal contraction of the anterior pelvic floor occurs during defaecation in patients with outlet obstruction constipation, then they may also have features of obstructed urinary flow.

Patients and methods

Ten consecutive female patients with typical symptoms of outlet obstruction constipation were studied (group 1). Seven attributed the onset of their symptoms to childbirth and three to hysterectomy All the patients had prolonged colonic transit times as indicated by the presence of at least four radiological markers in the rectosigmoid 5 days after the ingestion of 20 markers In addition, they failed to open the anorectal angle and evacuate liquid barium from the rectum during videoproctography. These study patients were compared with ten age- and sex-matched controls who had no gastrointestinal symptoms (group 2).

The study patients were first asked to void urine into a urometer and the peak flow rate, voided volume and voiding time were recorded They were then catheterized with a size 8 Fr double lumen catheter and the residual volume measured. Filling and voiding cystometry was then performed.

In control subjects only the peak flow rate, voided volume and voiding time were recorded since it was considered unethical to catheterize healthy women to obtain information which has already been established in the literature[6,7]

It has been demonstrated previously that both the peak flow rate and voiding time are dependent upon the intravesical prevoiding volume[8] We have therefore used the nomogram for normal females developed by Haylen *et al* [8] for reference purposes in the analysis of our results

Statistical analysis of peak flow rate and voiding time for the study group and controls was undertaken using a Mann–Whitney *U* test

Results

Eight of the ten patients with outlet obstruction constipation had urinary symptoms (urinary delay, 6, incomplete emptying, 5; nocturia, 4; stress incontinence, 3 patients)

The mean(s.e.m.) peak flow rate for the study patients was 19·4(6·4) ml/s The corresponding value for control subjects was significantly higher at 32 1(7·2) ml/s, $P<0{\cdot}05$ (*Figure 1*). The mean(s.e.m.) voiding time for group 1 was 62·9(23·7) s while the corresponding value in group 2 was 15·6(6) s, $P<0{\cdot}05$ (*Figure 2*). Nine of the ten controls voided urine within 30 s; in contrast, nine of the 10 study patients exceeded this value

The relationship between peak flow rate and intravesical prevoiding volume is shown in *Figure 3*. Despite an increasing intravesical volume, nine of the ten control subjects voided urine within the accepted upper limit of normal of 30 s. In contrast, nine of the ten patients with obstructed defaecation

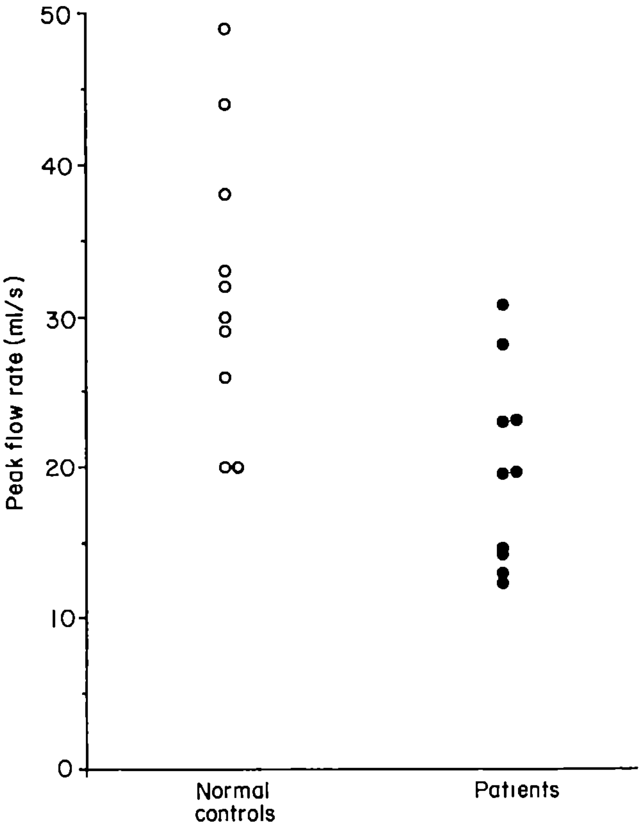

Figure 1 *Peak flow rates for patients with outlet obstruction constipation* (●) *and controls* (○). $P<0{\cdot}05$

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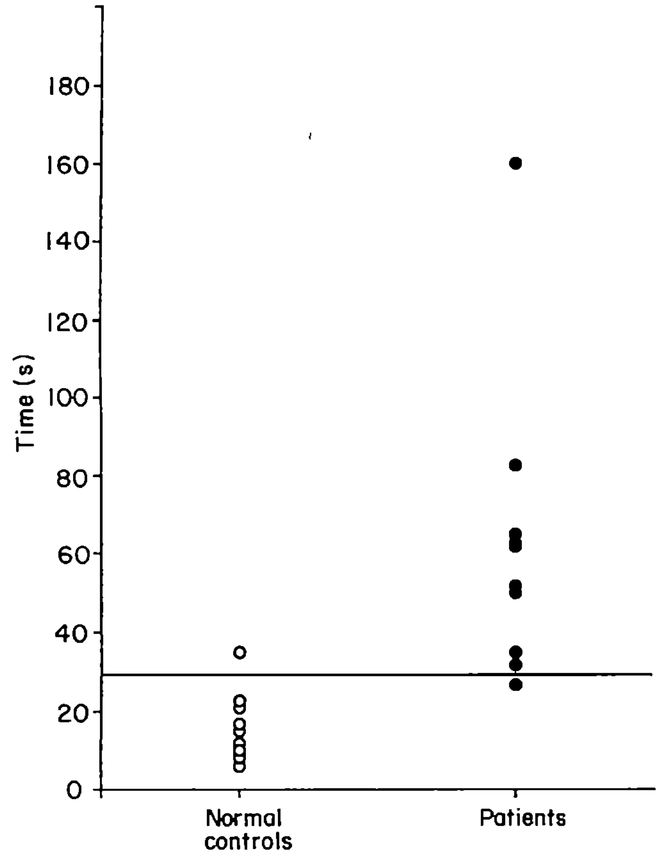

Figure 2 *Voiding times for patients with outlet obstruction constipation (●) and controls (○) The line marked at 30 s represents the accepted upper limit of normal* $P<0.05$

failed to do so. This difference in peak flow rate between study and control groups is emphasized when the female nomogram is included for reference (*Figure 4*).

The mean(s.e.m.) bladder volume for patients in group 1 was 482(80) ml. The corresponding value for control subjects was 254(112) ml, $P<0.03$. The mean residual volume following voiding was 44·6 ml (range 10–150 ml) in patients with obstructed defaecation, exceeding the expected normal of less than 10 ml in nine of the ten patients.

The bladder-filling profiles for patients with obstructed defaecation were normal and there was no evidence of detrusor instability. The mean(s.e.m.) detrusor pressure during the voiding phase was 53·3(12) cmH_2O.

Discussion

Clinicians are increasingly recognizing a group of predominantly female patients with symptoms of outlet obstruction constipation[1] Although the exact pathophysiology of this condition is unknown, it has been shown that these patients fail to open the anorectal junction and have inappropriate contraction of the puborectalis muscle on straining at stool[3]. The latter has been considered to be the primary anomaly and therapy has been directed toward this by division[9] or paralysis[10]. More recently it has been demonstrated that the levator fails to open the anorectal angle after the instillation of fluid. This raises the possibility that paradoxical contraction of the puborectalis muscle occurs as a result of loss of the countertraction of the posterior pelvic floor[11].

In this study we have assumed that the control subjects in group 2 had normal filling cystometrograms. Consequently no allowance has been made for a small residual volume which may have been present. We feel that this is acceptable since these women had no urinary symptoms and would therefore have been expected to have an insignificant residual volume following micturition.

The results of this study demonstrate that patients with outlet obstruction constipation also have difficulty in voiding urine. They have a lower peak flow rate, prolonged voiding time, raised intravesical prevoiding volumes and increased residual volumes when compared with age-matched controls. Since these patients have normal detrusor function it would appear that the reduced urinary flow results from outlet obstruction. It has previously been suggested that normal micturition requires the coordinated contraction of the posterior pelvic floor and that damage to the levator ani during childbirth could lead to retention of urine post partum[12]. This

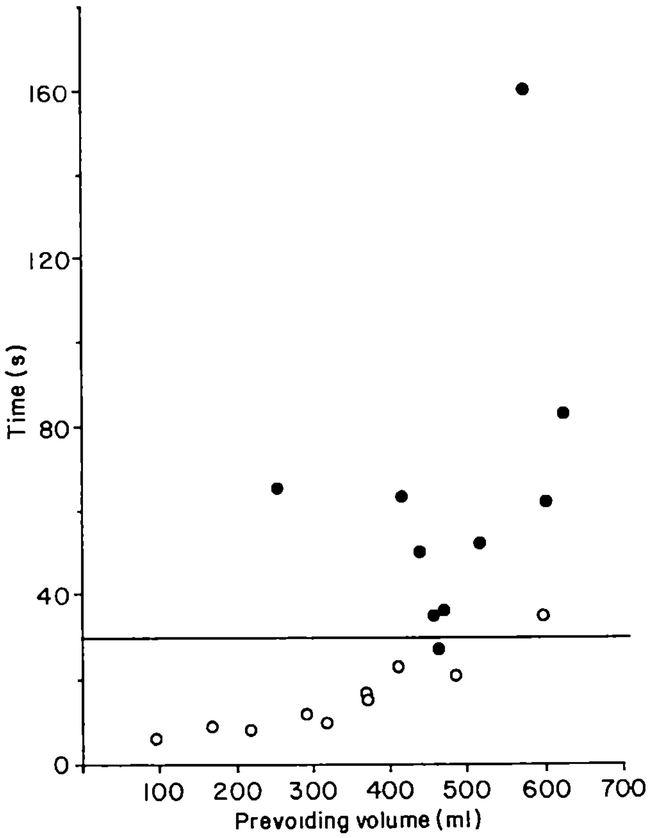

Figure 3 *Voiding time against prevoiding volume for patients with outlet obstruction constipation (●) and controls (○) The line marked at 30 s represents the accepted upper limit of normal*

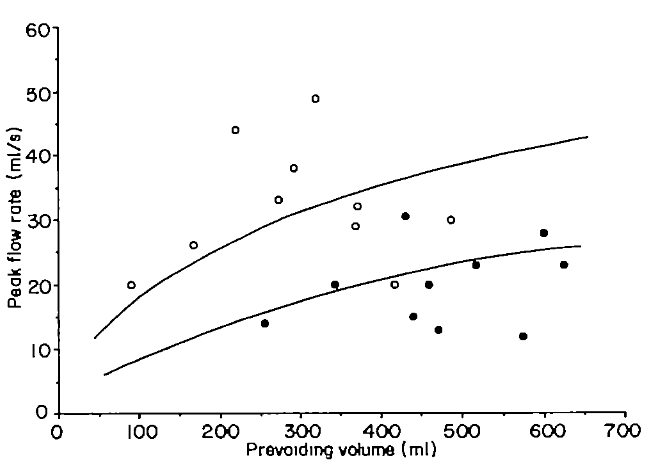

Figure 4 *Peak flow rate against prevoiding volume for patients with outlet obstruction constipation (●) and controls (○) The upper and lower line represent the 50th and the 5th centile respectively of the Liverpool nomogram for normal women*

may be due to unopposed contraction of the puborectalis during micturition. Alternatively, if these patients have failure of the posterior pelvic floor as the primary anomaly, this may result in posterior rotation of the bladder and incorporation of bladder neck into the anterior bladder wall. This configuration is known to result in reduced urinary flow[12,13].

An association between colonic dysfunction and abnormal bladder function has previously been noted[14–17]. Urodynamics performed on a group of patients with colonic inertia showed an increased bladder capacity with reduced vesical and rectal sensitivity but failed to show any reduction in flow rate[17]. This is in contrast with the present study. A possible explanation for this is that patients in previous studies were selected on the basis of prolonged transit studies alone and may not have included a homogeneous group of patients with outlet obstruction constipation.

The clinical presentation of constipation means different things to different people[18] and may have several aetiologies[18–23]. Constipation has a multifactorial basis and may result from slow transit[2], outlet obstruction[3,4], a hyperactive segment at the rectosigmoid[23], abnormally high sphincter pressures[17,18] or a combination of these factors. We have identified a specific group of women who have symptoms and radiological appearances of outlet obstruction constipation. These patients also have features of obstructed urinary flow, indicating an interrelationship between bladder and rectal dysfunction in this condition. This observation suggests that there may be a generalized pelvic floor disorder.

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Evaluation of diagnostic peritoneal lavage in suspected penetrating abdominal stab wounds using a dipstick technique

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The total protein content (g/l) and white blood cell count (cells/mm^3) of diagnostic peritoneal lavage was assessed using a urine dipstick in 46 patients with suspected penetrating abdominal stab wounds and equivocal physical examination. Those patients with a protein content $\geqslant 1$ g/l and white blood cell count of >500 cells/mm^3 were submitted to laparotomy while those with lower values underwent observation and repeat physical examination. In all, 26 patients had a positive lavage and significant injuries were found in 23 of these. Of 18 patients with a negative lavage, 17 were managed successfully without operation while one patient died from complications related to central venous catheterization. In two patients the lavage results were equivocal. One underwent a negative laparotomy and the remaining patient recovered uneventfully. The test has a 100 per cent sensitivity and 86 per cent specificity and provides an accurate, cheap, and rapid means of diagnosis of intra-abdominal injury in penetrating trauma.

Although designed primarily for use in patients with blunt abdominal trauma, diagnostic peritoneal lavage has gained acceptance for the investigation of patients suffering penetrating abdominal trauma[1–10]. However, contrary to its use in blunt trauma, no one set of standard quantitative criteria can be proposed owing to the much wider spectrum of injuries encountered, and because there is some debate on what constitutes a positive lavage.

Previous work from this institution highlighted the shortcominigs of cell counting of diagnostic peritoneal lavage in penetrating trauma and reported the much higher accuracy employing protein electrophoresis of the lavage effluent[11]. The results of this study showed a sensitivity of 78 per cent and specificity of 55 per cent using a white blood cell count of 500 cells/mm^3 to indicate significant injury, while the albumin levels between positive and negative laparotomy groups showed demarcation at the value of 1 g/l of lavage effluent with a diagnostic accuracy of 90 per cent. Although highly reliable this test is not without its disadvantages. A laboratory technician is required outside normal working hours, 80 per cent of trauma admissions occurring during this period. The equipment, although routinely available in most biochemistry laboratories associated with major hospitals, is not universally available and is expensive.

In an effort to overcome these problems and in an attempt to find a cheap and readily available alternative, the use of a dipstick technique was investigated.

The Combur-9-Test (Boehringer Mannheim Diagnostics, Germany) has been used routinely to evaluate urinary constituents. Two of the strip reagents measure the protein content and white blood cell count. The former demonstrates colour changes at 0·3, 1·0, and 5 g/l of protein, while the latter changes colour at white blood cell counts of 25, 75, and 500 cell/mm^3, the last mentioned being the standard value in diagnostic peritoneal lavage. Although described as measuring the total protein content, the reagent strip is most sensitive to albumin as this is the commonest urinary protein in pathological conditions of the renal tract. The colour changes on the dipstick were compared with absolute albumin values determined by protein electrophoresis of the peritoneal lavage effluent in the last 17 patients of our previous study[11]. These correlated closely, the dipstick producing a diagnostic accuracy rate of 94 per cent when compared with the operative findings.

A prospective study was undertaken therefore to determine whether assessment of the albumin and white blood cell concentrations of the lavage effluent using a dipstick technique was a reliable method of identifying intra-abdominal injury in patients with suspected penetrating trauma following stab wounds in whom the clinical findings were equivocal

Patients and methods

During the 6-month period September 1988–February 1989, 157 patients with stab wounds of the abdomen were admitted by one of three trauma teams to King Edward VIII Hospital, Durban The abdomen was defined anatomically from nipple line to pubis anteriorly and from inferior scapular angle to lower buttock crease posteriorly. Wound sites were divided into anterior (costal margin-pubis), anterosuperior (nipple line-costal margin), flank (anterioposterior axillary lines), and posterior (medial to posterior axillary line). Patients were divided into three groups on the basis of physical examination. Group A ($n=66$) underwent immediate laparotomy (shock, disembowelment, peritonitis, omental protrusion through a chest wound, haematemesis, blood *per rectum*). Group B ($n=41$) underwent observation and repeat examination (normotension, tenderness confined to wound). Group C ($n=50$) comprised those patients with an equivocal physical examination in whom intra-abdominal injury could neither be confirmed nor excluded (tenderness distant from wound without peritonitis, normotension) and these formed the study group

There were 46 men and four women, with an age range of 16–35 years (mean 23·6 years) Stab wounds involved the anterior abdomen in 25 patients, the flank in eight patients, were above the costal margin in seven patients, and were posterior in six patients Four patients had suffered multiple stab wounds

Diagnostic peritoneal lavage was performed using the closed guidewire technique[12]. The lavage effluent was tested with a Combur-9 dipstick. A positive lavage was defined as one in which the protein content was $\geqslant 1$ g/l and the white blood cell count was >500 cells/mm^3 as indicated by colour changes on the dipstick. A lavage was considered negative if the protein level and white blood cell count were below the respective levels, and equivocal if one observation was positive but the other negative. Those patients fulfilling the criteria for a positive lavage underwent laparotomy, while those with a negative or equivocal lavage underwent observation and repeat physical examination. The lavage

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Table 1 *Operative findings in 26 patients with positive peritoneal lavage*

Laparotomy					
Positive		Non-therapeutic		Negative	
Injuries*	*n*	Injuries	*n*	Findings	*n*
Small intestine alone	11	Mesentery	1	Pelvic inflammatory disease	1
Colon and small intestine	3			Tuberculosis	1
Colon alone	2				
Stomach alone	2				
Stomach and small intestine	1				
Liver and small intestine	1				
Liver and diaphragm	1				
Liver, diaphragm and stomach	1				
Stomach, colon and small intestine	1				
Total	23		1		2

* All hollow visceral injuries involved intestinal perforation

results were then compared with the operative findings and outcome of obervation

A laparotomy was considered positive if repair or drainage of a damaged viscus was required, negative if peritoneal penetration had not occurred, and non-therapeutic if penetration alone or penetration with insignificant visceral damage was found.

Results

Four patients were excluded from the study because of a heavily blood stained lavage effluent. This stained the dipstick to such a degree that the colour change could not be read accurately. The remaining 46 patients were entered into the study. There were 26 positive, 18 negative, and two equivocal lavage results.

Positive lavage (n = *26*)

All patients were submitted to laparotomy; this was positive in 23 (*Table 1*). Fifteen patients had a single organ injury, six had sustained double organ injury, and the remaining two patients each had three organs injured. Contamination was considered minimal in all cases. In the remaining three patients one laparotomy was non-therapeutic (penetration with mild haemoperitoneum from a minor mesenteric laceration). Penetration had not occurred in the other two patients and according to the criteria these were therefore regarded as negative laparotomies. However, one patient was found to have severe pelvic inflammatory disease with free pus in the pouch of Douglas, while in the other multiple nodules were present throughout the peritoneal cavity, the histology of which revealed active tuberculosis. There were no deaths in this group.

Negative lavage (n = *18*)

Seventeen patients recovered without operation. One patient in this group died. He had suffered multiple stab wounds of the posterior chest and abdomen resulting in bilateral pneumothoraces and an equivocal abdominal examination. Repeat examination revealed an ileus without signs of peritonitis. Gastrografin® (Schering AG, Berlin, Germany) meal excluded a retroperitoneal duodenal injury and showed distortion of the duodenal loop compatible with retroperitoneal haematoma Following insertion of a subclavian central venous catheter he became extremely dyspnoeic. Chest radiography revealed a large effusion The catheter was removed and an intercostal drain inserted but he suffered a cardiorespiratory arrest with unsuccessful resuscitation. Post-mortem examination revealed a small posterior renal parenchymal laceration with a surrounding retroperitoneal fasciitis. No other visceral injury was demonstrated.

Equivocal lavage (n = *2*)

In both patients the lavage protein levels were between 1–5 g/l but the white blood cell count was <500 cell/mm^3. Laparotomy was undertaken in one patient because of increasing abdominal tenderness. The weapon had not penetrated the peritoneal cavity and a mild alcohol-induced acute pancreatitis was the only abnormality found. Recovery without operation occurred in the remaining patient.

Using this investigation to detect intra-abdominal injury there were 23 true positive, 3 false positive, 18 true negative, and no false negative results (excluding equivocal lavage). This produces a sensitivity of 100 per cent, a specificity of 86 per cent, a positive predictive value of 88 per cent and a negative predictive value of 100 per cent.

Discussion

Negative laparotomy for abdominal trauma is associated with significant morbidity and mortality[13–17] As many as 40 per cent of patients with abdominal stab wounds do not require surgery for their injuries and many surgeons have adopted a selective conservative policy of management based on clinical examination. Originally proposed by Shaftan[17] this has been shown repeatedly to be a safe and reliable form of treatment[18–24].

There are, however, a number of patients in whom repeated physical examination remains equivocal but significant injury cannot be excluded, and in this group the negative laparotomy rate remains high[11]. Repeated physical examination over a number of hours may ultimately demonstrate the need for operative treatment but this has a number of disadvantages First, it is time consuming and in a busy trauma centre may not be feasible on a regular 2-hourly basis. Second, repeat examination should be performed by the same person to exclude observer variation. Third, analgesia must be withheld from the patient to prevent the masking of changing signs In an attempt to overcome these problems other methods of investigation have been proposed. Contrast radiography[25,26], local wound exploration[1,8], and diagnostic peritoneal lavage employing cell counting[1–10] may identify penetration but do not confirm visceral injury. Indeed, the lack of uniform agreement among authors as to what constitutes a positive lavage is a problem of using this method in patients with penetrating trauma. Computed tomographic (CT) scanning[27] has been shown to be reliable in detecting penetration and solid organ injury but unreliable in confirming hollow organ damage. It is an expensive investigation and as this study demonstrates, the majority of patients with an equivocal physical examination and significant injury have suffered perforation of a hollow viscus

CT scanning in this situation is therefore superfluous, time consuming, extravagant, and unreliable.

Experimental work suggested the use of protein markers as an aid in diagnosing hollow visceral injury[28] and clinical studies have confirmed these findings[11] Although highly accurate this still requires laboratory facilities and expensive equipment. The use of a dipstick technique, employing previously ascertained criteria as markers of intra-abdominal injury has been found in this study to be highly accurate, and provides an instant result at the bedside.

The absence of any false negative results accounts for the 100 per cent sensitivity and 100 per cent negative predictive value. However, as laparotomy was not undertaken in all patients the possibility of missing a diaphragmatic injury must be considered. In our previous study[11] three patients with pure diaphragmatic injuries all had protein levels of <1 g/l Of the 46 patients entered into the present study six suffered low chest wounds, four in the negative and two in the positive lavage group, the latter both sustaining wounds of the diaphragm but in combination with other visceral injuries. Until a specific marker can be isolated for this lesion it will remain a major problem of diagnosis, although the use of low red blood cell counts in diagnostic peritoneal lavage may improve accuracy[10]

Diagnostic peritoneal lavage in whatever form has the major disadvantage that it is unreliable in patients with posterior stab wounds[29]. Six patients in this series presented with posterior stabs all of whom were in the negative lavage group. One patient died, and although this was not the result of missed hollow visceral injury, the possibility of necrotizing infection in the retroperitoneal tissues, as described by Whalen *et al.*[30], must always be considered. Diagnostic lavage as a means of excluding injury should not be employed in these patients. Clinical examination repeated as necessary, has been shown to be a safer method of assessment[30,31], although CT scanning may prove more accurate[27]

A further disadvantage of the dipstick method occurs when the effluent is heavily blood stained. This causes staining of the reagent strip and the underlying colour change cannot be visualized. In this situation reliance must be placed on serial physical examination.

Employing the dipstick technique has resulted in a reduction in the negative laparotomy rate in patients with an equivocal physical examination from 26 per cent to 12 per cent in our institution. The technique is safe, cheap and provides an immediate answer at the bedside It may be used in hospitals lacking specialized laboratory facilities for either cell counting or protein electrophoresis and as such is applicable to both major trauma centres and district hospitals.

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Early abdominal complications following heart and heart–lung transplantation

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In the first 11 years of the heart and heart–lung transplantation programme at Papworth Hospital, Cambridge, 356 patients underwent heart transplantation, and 73 patients received both heart and lungs. Out of 429 patients 41 (9·5 per cent) developed abdominal complications within the first 30 days, and 20 of the 41 required surgery. The complications included pancreatitis (10), peptic ulceration (8), and pseudo-obstruction (8), in addition to colonic perforation and small bowel obstruction. When laparotomy was performed it was well tolerated. This paper supports the view that successful management of abdominal complications following transplantation requires prompt diagnosis and treatment. Where doubt exists in the presence of an acute abdomen, laparotomy is the appropriate way to establish a definitive diagnosis.

Between 1979 and 1989, 356 patients received orthotopic cardiac transplants at Papworth Hospital, nine receiving more than one graft; a further 73 patients underwent transplantation of heart and lungs. Many of these patients developed abdominal complications within the first 30 days, causing significant morbidity. This paper reviews these complications, their presentation and their management.

Patients and methods

The records of those patients undergoing transplantation of heart, and heart and lungs, between 1979 and 1989 at Papworth Hospital were reviewed. Any patient developing significant abdominal symptoms meriting surgical consultation while still an inpatient within 30 days of transplantation was recorded. All patients were immunosuppressed with a combination of prednisolone, azathioprine, and cyclosporin A (see *Table 1*). The immunosuppression protocol changed with the introduction of cyclosporin A, which was used first in combination with prednisolone or azathioprine, and finally with both as triple therapy Prophylactic antithymocyte globulin was used throughout the programme over the initial post-transplant period.

Results

Forty-one patients (9·5 per cent) developed abdominal symptoms, of these 20 required surgery The overall 30 day mortality was also 41, and of these patients six (15 per cent) had abdominal symptoms, although only four died as a direct result of them, the other two deaths being due to rejection and graft failure. Hence abdominal complications caused significant early morbidity, and four out of 41 (10 per cent) of the total early mortality. The 12 month actuarial survival for those patients with abdominal symptoms and for heart transplantation overall is compared in *Figure 1* There is no significant difference. A reduction in survival after heart–lung transplantation was also seen, but was not significant. The abdominal conditions are detailed in *Table 2*, and are outlined below.

Pancreatitis

Ten patients developed pancreatitis In two the serum amylase was normal and the diagnosis was subsequently made at laparotomy. In two, pancreatitis developed in association with cytomegalovirus (CMV) infection, at 23 and 24 days after transplantation. In the others the mean time of onset was 12 days after transplantation (see *Figure 2*). Four other patients died from graft failure after prolonged hypotension (secondary to rejection in two) and were found at autopsy to have severe pancreatitis; in two there were associated ulcers in the stomach and oesophagus. There were similar numbers of patients on each of of the four drug regimes, with pancreatitis developing equally in the absence of steroids, azathioprine and cyclosporin A.

Peptic ulceration

Apart from the autopsy findings mentioned above, eight patients developed peptic ulcers (six duodenal, two gastric), manifesting as haemorrhage or epigastric pain. Diagnosis was proven by endoscopy, barium meal or both. All but two were on prednisolone at the time of onset of symptoms, and two were also taking non-steroidal anti-inflammatory drugs for arthritis before transplantation. All were treated with ranitidine in the first instance. Only one failed to respond and had a significant rebleed requiring laparotomy A vagotomy was performed, the bleeding vessel undersewn, and the duodenotomy closed in a T-fashion as a pyloroplasty. This pyloroplasty dehisced 8 days later at the apex of the 'T', necessitating a further laparotomy at which it was repaired. The patient remains well 5 years later.

Pseudo-obstruction

Eight patients developed a syndrome of increasing constipation with abdominal pain and distension between 2 and 8 days (mean 5 days) after transplantation. Abdominal radiographs confirmed a dilated right colon mimicking distal obstruction All patients had a leucocytosis and none was subsequently shown to have an obstructing colonic lesion on barium examination. Initial management comprised suppositories and enemata. Two failed to respond and went on to perforate their colons. One had a caecal perforation treated by right hemicolectomy and primary ileotransverse anastomosis; the other had a caecostomy performed which enabled a perforation in the distended transverse colon to be identified It was exteriorized as a transverse loop colostomy and closed uneventfully 3 months later. A third patient had a laparotomy on day 3 at which the colon was decompressed retrogradely. He subsequently developed graft-versus-host disease (see below).

Perforated diverticular disease

Two patients had laparotomies for perforated sigmoid diverticula. Neither had signs of peritonitis at the time of diagnosis, the indication for surgery being the demonstration of a pneumoperitoneum on chest radiography One, with faecal peritonitis, had an immediate sigmoid colectomy with fashioning of a Paul–Mikulicz colostomy, which was closed

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Table 1 *Immunosuppression*

Regimen*	Dates	Prednisolone Initial dose 1 mg kg^{-1} day^{-1} Maintenance 0·25 mg kg^{-1} day^{-1} HL 375 mg for 1 day only	Azathioprine 1–2 mg kg^{-1} day^{-1} Maintain. leucocyte count $<9 \times 10^9$/l	Cyclosporin A 8–10 mg kg^{-1} day^{-1} Maintenance: plasma level 600–900 mg l^{-1}
A	Jan 1979– March 1982	+	+	–
B	1982–1985	+	–	+
C	1982–1985	–	+	+
D	since 1985	+	+	+

* All patients received equine antithymocyte globulin for 28 days after transplant if not on cyclosporin A (regimen A), and for 3 days if on cyclosporin A (regimen B, C, and D). HL, heart–lung

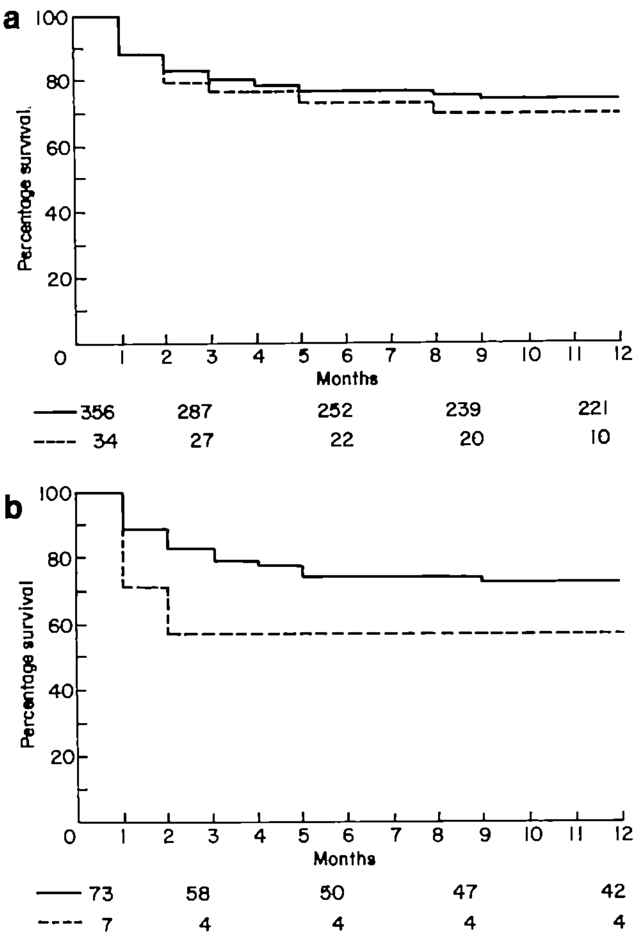

Figure 1 *Overall survival following transplantation compared with survival of patients with abdominal complications* **a** *heart transplantation and* **b** *heart–lung transplantation.* ——, *All patients;* ----, *patients with abdominal complications*

uneventfully. The second had no evidence of faecal soiling so the site of perforation was oversewn and defunctioned by a proximal transverse loop colostomy. Persistent leakage demonstrated on subsequent barium examinations necessitated a sigmoid colectomy before the colostomy could be finally closed

Intestinal obstruction

Five patients had small bowel obstruction. One had an obstructed paraumbilical hernia repaired on day 25, another had a right hemicolectomy for a caecal volvulus on day 8, the bowel being brought out as an ileocolostomy which was closed 3 months later; three patients who had had heart–lung transplants for cystic fibrosis also developed small bowel obstruction. One of these three had a small bowel volvulus resected on day 9 with primary anastomosis; the other two developed vomiting, distension and pain. One vomited and aspirated on day 5. His abdominal pain worsened and a laparotomy was performed at which obstruction was found to be due to tenacious enteral contents. The bowel was decompressed but the patient died the following day from aspiration pneumonia. The second patient was successfully treated by nasogastric aspiration and intravenous fluids.

Other/undiagnosed

One patient underwent a laparotomy for severe epigastric pain after a difficult heart transplant for rheumatic heart disease. Cardiopulmonary bypass had been established via the right femoral vessels and she subsequently developed a phlebitis and cellulitis around the wound. A swab from the wound grew *Staphylococcus aureus* and 1 week later she developed septicaemic shock requiring inotropic support Her abdomen became distended and painful, with features of peritonitis so, fearing an intra-abdominal catastrophe, a laparotomy was performed. Blood-stained fluid (800 ml) was found but no macroscopic pathology. The fluid had an amylase concentration of 77 units/l with no microbiological growth. Subsequently *S aureus* was cultured from her blood.

One patient developed epigastric pain radiating to his back. Upper gastrointestinal endoscopy was normal, and his serum amylase concentration was 230 units/l Following increasing pain, and with evidence of dilation of the common bile duct on ultrasonography, a laparotomy was done The gallbladder was tense and distended and a cholecystectomy was performed. Subsequent histology of the gallbladder was normal He died 10 days later from graft rejection.

Urological

A 59-year-old man went into urinary retention secondary to benign prostatic hyperplasia following heart transplantation for ischaemia He required a transurethral prostatectomy which was uneventfully performed on day 30.

Mesenteric ischaemia

Four patients developed pain due to mesenteric ischaemia Two who received heart transplants for end-stage ischaemic heart disease became symptomatic shortly after surgery One became confused and drowsy on day 3 and developed increasing abdominal distension on day 5 At laparotomy extensive infarction from jejunum to mid-colon was found. No resection was undertaken and he died later the same day. Autopsy revealed a thrombosed superior mesenteric artery. The second patient developed pain on day 2, and laparotomy on day 4 revealed necrotic ileum and proximal colon which were resected, the ends being left as an ileocolostomy. His condition deteriorated and he died 6 days later. Autopsy revealed patent mesenteric vessels, with patchy necrosis of the remaining large bowel and severe acute pancreatitis.

Table 2 *Patients with abdominal symptoms*

Complication	Total no of patients	Heart	Heart–lung	No. of operations§	Deaths† within 30 days
Pancreatitis	10(+4)*	9(+4)*	1	2	–
Peptic ulcer	8	8	–	1	–
Pseudo-obstruction	8	7	1	3	0‡
Perforated diverticula	2	2	–	2	–
Volvulus	2	1	1	2	–
Mesenteric infarction	4	3	1	4	4[a]
Obstructed hernia	1	1	–	1	–
Meconium ileus equivalent	2	–	2	1	1
Colonic ulceration	2	–	2	2	0‡
Urinary retention	1	1	–	1	–
Cholecystectomy	1	1	–	1	1[b]
Staphylococcal septicaemia	1	1	–	1	–

*Four patients had evidence of pancreatitis at autopsy, including one dying from mesenteric infarction, values in parantheses denote diagnoses made at autopsy, †four due directly to their abdominal complication, the others due to graft failure[a] and rejection[b], ‡one died on day 32 with probable graft-versus-host disease, §two patients had two operations, one requiring re-exploration after surgery for peptic ulcer, the other having pseudo-obstruction and later graft-versus-host disease (*Table 4*)

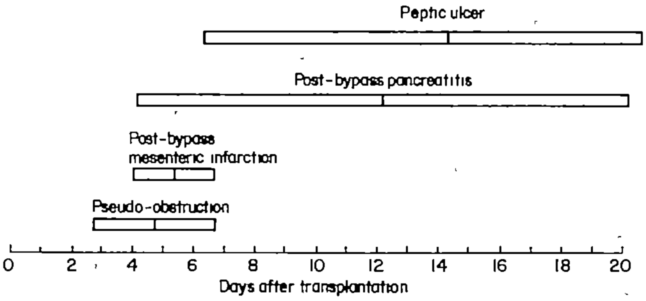

Figure 2 *Temporal relationship of abdominal complication to transplantation. Results are mean(s d.)*

The third patient, aged 45 and with a cardiomyopathy, developed severe rejection of his heart graft on day 12. His cardiac output remained poor in spite of inotropes and retransplantation was considered, but in the interim he developed *Pneumocystis* pneumonia. On day 25, following increasing abdominal distension, a laparotomy was performed and revealed extensive mesenteric infarction. No resection was undertaken and he died shortly after. Again autopsy showed patent mesenteric vessels.

The last patient (No. 19) had a laparotomy and resection of an extensive small bowel infarction on day 7 following transplantation. He had received a single lung transplant after he developed obliterative bronchiolitis in the heart–lung graft which he had received 2 years previously. The original graft was for pulmonary hypertension secondary to recurrent pulmonary emboli associated with systemic lupus erythematosis. Histology of the resected bowel revealed no evidence of thrombosis or vasculitis. Unfortunately he died 11 days later following a cardiac arrest. Autopsy revealed no abnormality in the mesenteric vessels, but extensive consolidation of the new lung. Unlike the previous three patients with mesenteric ischaemia he did not develop a leucocytosis – indeed his leucocyte count fell from 7·1 to 1·1 × 10^9/l in spite of reduction in immunosuppression. CMV was not detected.

Hence in all four patients infarction followed periods of ischaemia, either related to bypass or to graft failure.

Colonic ulceration with bleeding or perforation

In addition to patient No. 19 (above), two other patients developed colonic conditions requiring laparotomy associated with a falling leucocyte count. One had a heart–lung transplant for pulmonary fibrosis secondary to sarcoidosis. An episode of melaena on day 23 was followed by increasing abdominal pain. A laparotomy was performed and an oedematous caecum was resected and an ileocolostomy fashioned. His leucocyte count had fallen from 8 to 1·9 × 10^9/l. He subsequently developed CMV pneumonitis, was treated with ganciclovir, but died on day 85.

The last patient developed pseudo-obstruction 3 days after transplantation, requiring operative decompression. On day 10 he experienced further abdominal pain. Abdominal radiography still demonstrated intraperitoneal gas but he had no signs of peritonism. His leucocyte count then was 9·8 × 10^9/l. Over the next 9 days it fell to 0·15 × 10^9/l, his pain worsened, he became pyrexial (39°C) and he developed a generalized maculopapular rash. He underwent a further laparotomy at which a thickened and ulcerated colon was found with a perforation of the midtransverse colon A right hemicolectomy was performed with formation of an ileocolostomy. Histology showed extensive ulceration, with no evidence of CMV inclusions. Subsequent analysis confirmed that at the time of his leucopenia there was a predominance of donor lymphocytes in his peripheral blood He was treated with high dose methylprednisolone but died on day 32.

Discussion

Transplantation is now an accepted treatment for patients with end-stage cardiac and pulmonary disease Survival rates are now good; the 1- and 5-year actuarial survival rates for the 356 patients undergoing heart transplantation at Papworth since March 1982 are 79 and 66 per cent respectively While rejection and primary graft failure are the main causes of early death, a significant number of patients develop abdominal complaints. In this respect our experience is echoed by other smaller series, where 30 day morbidity rates from general surgical conditions vary from 7 to 13 per cent[1–4]. In our series the early (30 day) mortality was 9·5 per cent Comparison across published series is difficult due to differing criteria for inclusion and differing time intervals of follow-up Following cardiac surgery alone the incidence of general surgical problems is much less with incidences of up to 1·6 per cent being cited, with a mortality rate of up to 36 per cent[5,6].

Cardiopulmonary bypass (CPB) surgery is associated with pancreatitis, and it is no surprise that pancreatitis also occurs after the prolonged bypass entailed in heart and heart–lung transplantation Feiner noted that 15 per cent of patients dying

Table 3 *Twelve month survival and cardiopulmonary bypass time in patients receiving a heart or heart–lung transplant*

	Heart transplant		Heart–lung transplant	
	Total number	With abdominal complications	Total number	With abdominal complications
Number (% of total)	356	34 (9 5)	73	7 (10)
12 month actuarial survival (%)	79	68	74	67
Mean(s.d.) cardioplumonary bypass time in minutes	94(31)	103(25)	138(28)	—

after CPB had evidence of pancreatitis at autopsy (10 per cent in our study)[7] She believed that it was related to ischaemia and hypothermia during bypass. In the present series most patients developing pancreatitis within the first 30 days did so early after transplantation, although their CPB time was not significantly longer than the other patients in the series (*Table 3*). The two who developed it later (mean 23 days) after transplantation had cytomegalovirus infection. When pancreatitis is associated with CMV it is frequently severe and with high morbidity and mortality rates.

All four patients who had pancreatitis diagnosed at autopsy, one of whom had had a resection for mesenteric infarction, had protracted periods of ischaemia and inotrope administration for failing grafts. It is important to note that in addition to those cases where the diagnosis was made at autopsy, two others presented with a normal serum amylase They were diagnosed at laparotomy. The difficulty in making a positive diagnosis and the incidence of normal serum amylase in the presence of inflammation make management difficult. The authors recommend early computed tomographic scanning and laparotomy where diagnostic doubt exists. Early laparotomy to resolve diagnostic doubt is preferable to delay and the risk of generalized peritonitis in an immunocompromised patient.

While ischaemic and viral aetiologies for early pancreatitis could be an explanation, pancreatitis has also been associated with prednisolone and azathioprine[8]. However, there was no significant difference in incidence between different immunosuppressive regimes in our series, although numbers are small.

Gastric and duodenal ulceration is common following bypass surgery, with gastrointestinal haemorrhage accounting for between 35 and 61 per cent of abdominal complications[5,6]. Transplantation involves two additional risk factors for ulceration, namely the presence of immunosuppressive drugs (notably prednisolone), and the possibility of ulceration as a manifestation of CMV infection. None of the patients with ulcers were identified as having CMV infection, and all but two were on prednisolone. All but one responded to conservative treatment The one who did not respond required reoperation after a suture line breakdown of his pyloroplasty, highlighting the difficulty of obtaining healing of high-risk suture lines in immunosuppressed patients. A similar complication was reported by Villar *et al.*[9].

We have described eight patients who developed colonic pseudo-obstruction between 3 and 8 days after operation. When Ogilvie described this syndrome in 1948 he attributed it to an imbalance in the autonomic supply to the distal colon resulting from sympathetic denervation secondary to malignant infiltration[10]. Since his description many similar cases of proximal colonic distension in the absence of an obstructing cause have been reported[11]. Most resolve spontaneously after enemata or colonoscopy and few go on to perforate[12]. Why 1·8 per cent of our patients should develop the syndrome is unclear Although this complication has been reported after CPB, it is not common and this high incidence may reflect autonomic disturbance associated with removal of the heart. This, or an ischaemic aetiology would be supported by the close temporal relationship to surgery. It is possible that the type of postoperative analgesia may be significant; most of these patients were taking paracetamol and dextropropoxyphene. Pseudo-obstruction is also reported early following renal transplantation, and Stratta *et al* ascribe the high incidence of acute colonic ileus to high doses of steroids[13]. In their series reduction in steroid dosage, withdrawal of narcotic analgesics and intravenous fluid therapy corresponded with resolution in 77 per cent of patients. Of those who failed to respond, one perforated his caecum and subsequently died. The rest were successfully decompressed colonoscopically

Colonic pseudo-obstruction should be recognized early and treated aggressively. In heart transplant recipients reduction in immunosuppression is often not possible, but enemata and colonoscopy are advocated Regular radiographs are necessary to diagnose perforation early when it occurs, and elective surgical decompression should be considered if the condition fails to respond. Colon *et al.* report three patients with 'colonic ileus' of whom two were decompressed by colonoscopy and one died following caecal perforation[14] Early colonoscopy and laparotomy in unresolving pseudo-obstruction, with early recognition of perforation when it occurs, are essential for the successful management of these patients.

Table 4 details those patients undergoing laparotomy As a group the 20 patients tolerated laparotomy well. This has also been true of patients undergoing surgery at a later time after transplantation, when we have performed procedures including cholecystectomy, abdominoperineal excision of rectum and abdominal aortic aneurysm resection without significant morbidity and without mortality. When death occurred in the early group, two patients had extensive bowel necrosis which was unresectable. The patient who died with 'meconium ileus equivalent' (see below) had already aspirated before surgery and aspiration pneumonia was confirmed at autopsy. The other deaths were due to graft failure and not related to laparotomy The occurrence of perforation of sigmoid diverticula has been discussed elsewhere[15]. These two cases are important because of their presentation with relatively minor symptoms and minimal signs. Early laparotomy was successful. The failure of one patient to seal his perforation after defunctioning and oversewing is probably related to immunosuppression; the authors recommend exteriorizing the bowel when contamination with colonic contents is possible, or bowel viability is in question.

Five patients developed small bowel obstruction Of these two had cystic fibrosis In addition to their pulmonary problems these patients have pancreatic exocrine failure and their enteric secretions tend to be more viscid than normal. These viscid secretions can cause a syndrome of distal small bowel obstruction, otherwise known as 'meconium ileus equivalent' (MIE)[16]. As more patients undergo heart–lung transplantation for cystic fibrosis the problem of MIE may be more frequently anticipated. If simple nasogastric aspiration is unsuccessful, instillation of *N*-acetylcysteine is worthwhile to break down the viscid secretions. This is now given as routine postoperative prophylaxis in our unit. However, the possibility of alternative causes for obstruction should be borne in mind, such as volvulus and intussusception both of which are commoner in patients with cystic fibrosis. A negative laparotomy is better tolerated than peritonitis or ischaemic bowel; however, small bowel

Table 4 *Patients undergoing surgery following transplantation*

Patient number	Age	Transplantation	Day after transplantation	Complication	Procedure	Outcome
Pancreatitis						
1	26	H	7	Abdominal pain	Laparotomy	Died day 1035, COD
2	52	H	19	Abdominal pain	Laparotomy	Died day 222, rejection
Bleeding duodenal ulcer						
3	20	H	34	Rebleed	Vagotomy and pyloroplasty	*Alive day 2134*
			42	Pyloroplasty dehisced	Resuture	
Pseudo-obstruction						
4	49	H	6	Perforated transverse colon	Exteriorization as colostomy	Died day 625, COD
5	27	H	8	Caecal perforation	Right hemicolectomy	*Alive day 730*
6	43	HL	3	Distension, no perforation	Laparotomy	
Perforated colonic diverticula						
7	51	H	11	Perforated sigmoid diverticula	Sigmoid colectomy and Paul–Mikulicz colostomy	*Alive day 1030*
8	51	H	3	Perforated sigmoid diverticula	Perforation oversewn, transverse colostomy	Died day 887; rejection
Obstruction						
9	55	H	25	Obstructed hernia	Paraumbilical hernia repair	Died day 666, COD
10	22	HL	5	Meconium ileus equivalent	Nasogastric decompression	Died day 6, aspiration pneumonia
11	28	HL	9	Small bowel volvulus	Resection	*Alive day 550*
12	48	H	8	Caecal volvulus	Right hemicolectomy Ileocolostomy	*Alive day 243*
Other/undiagnosed						
13	46	H	30	Abdominal pain	Normal laparotomy, *Staphylococcus* septicaemia	*Alive day 705*
14	53	H	17	Epigastric pain	Laparotomy and cholecystectomy	Died day 27, rejection
TURP						
15	59	H	30	Urinary retention	TURP	*Alive day 584*
Mesenteric infarction						
16	45	H	25	Mesenteric infarction	Laparotomy, no procedure	Died same day
17	55	H	4	Mesenteric infarction	Resection and ileocolostomy	Died day 10
18	55	H	5	Mesenteric infarction	Laparotomy, no procedure	Died same day
19	35	HL	7	Mesenteric infarction	Resection and ileocolostomy	Died day 18, cardiac arrest
Colonic ulceration and leucopenia						
6	43	HL	19	Perforated oedematous transverse colon	Right hemicolectomy and ileocolostomy	Died day 32, graft-versus-host disease
20	42	HL	23	Oedematous ulcerated caecum	Right hemicolectomy and ileocolostomy	Died day 85, CMV pneumonitis

COD, Coronary occlusive disease, CMV, cytomegalovirus; TURP, transurethral prostatectomy, H, heart, HL, heart–lung. Survival as at 2/3/90

resection in the presence of this condition is associated with a high incidence of anastomotic breakdown.

The occurrence of mesenteric infarction, associated with thrombosis in one patient, hypoperfusion in two and idiopathic in the fourth caused 100 per cent mortality. In two the affected bowel was so extensive it was unresectable, and death followed shortly afterwards. The third had a resection and ileocolostomy but his heart allograft finally failed due to rejection 2 days later. The fourth patient is part of a group of three patients who had colonic resections following the development of pain associated with leucopenia. One of this group probably had acute graft-versus-host disease. Reducing immunosuppression in response to the leucopenia was therefore inappropriate. Patient No. 20, who also developed pain and had a resection, died from CMV pneumonitis 85 days after transplantation. It is probable that leucopenia was a manifestation of CMV infection, although no inclusions were found on histological examination. CMV-associated colonic perforation has been reported previously after heart transplantation and caecal ulceration recognized after renal transplantation[17,18]. In these cases reduction in immunosuppression is appropriate

Patient No 19 had an idiopathic mesenteric infarct Although there was no evidence of vasculitis, it is probable that this thrombosis was related to systemic lupus erythematosis since he had previously had thromboembolic pulmonary disease. Leucopenia was probably related to the presence of necrotic bowel, the usual leucocytosis being abolished by immunosuppression.

In summary, we report an extensive series of abdominal complications occurring early after heart and heart–lung transplantation. These can broadly be divided into three groups. Immediate complications occurring within the first week, including pseudo-obstruction, bypass related pancreatitis, MIE and mesenteric infarction, which are related to CPB and the high level of initial immunosuppression. In the latter part of the 'early post-transplant' period opportunist viral infections such as CMV-associated pancreatitis occur, as well as manifestations of rejection, either host-versus-graft, or graft-versus-host. Finally, throughout this early period there is a steady occurrence of complications such as gastrointestinal haemorrhage, diverticular perforation, volvulus and hernia obstruction

Diagnosis of abdominal complications may be difficult, especially by junior surgeons, since symptoms are difficult to evaluate in early postoperative patients, and abdominal signs and signs of sepsis may be masked by steroids Access to full diagnostic imaging modalities including barium radiographs, ultrasound, computed tomography and endoscopy are essential, as is review by an experienced surgeon. Patients tolerate laparotomy well, even immediately after transplantation, and it is preferable to establish a definitive diagnosis by laparotomy than risk extensive peritonitis in an immunocompromised patient. Close co-operation between cardiac and general surgeons is mandatory.

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Suture length to wound length ratio and the integrity of midline and lateral paramedian incisions

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A total of 349 patients were randomized to undergo laparotomy through a lateral paramedian incision with layered closure ($n = 137$)*, a midline incision with mass closure* ($n = 104$) *or a midline incision using layered closure* ($n = 108$)*, endeavouring to close the latter two incisions with a measured suture length to wound length ratio of greater than 4·1. After 18 months follow-up, no patient in the lateral paramedian group had developed an incisional hernia whereas 7 of 104 patients undergoing a midline incision with mass closure and 7 of 108 patients undergoing a midline incision with layered closure had incisional hernias* ($P < 0·01$). *The mean suture length to wound length ratios for the three groups were 2·6* (*range 1·3–6·2*), *5·0* (*range 3·0–8·7*) *and 3·7* (*range 2·0–6·3*) *respectively* ($P < 0·0001$). *The lateral paramedian incision remains superior to the midline incision closed with the mass technique and its integrity is independent of the suture length to wound length ratio.*

Previous studies of vertical abdominal incisions[1–7] have consistently found the lateral paramedian incision to have a lower incidence of incisional hernia than the midline incision. This is achieved at the expense of a small increase in operating time and a statistically insignificant rise in the incidence of wound infection[1,2].

Jenkins demonstrated that secure closure of a vertical abdominal incision is only possible if a ratio of suture length to wound length greater than 4:1 is achieved[8]. Previous trials comparing vertical abdominal incisions have been criticised for not measuring the wound length to suture length ratio. Poor results obtained with the midline incision were ascribed to poor surgical technique providing a suture length to wound length ratio of less than 4.1 and good results for the lateral paramedian incision have been attributable to a high suture length to wound length ratio.

The incidence of wound infection in abdominal incisions has been reduced by the use of staples for skin closure[9] and by the use of polydioxanone suture, which has been shown to have an incisional hernia rate equivalent to that of polypropylene[10,11].

A clinical trial was conducted to investigate the importance of suture length to wound length ratio achieved in the layered closure of the lateral paramedian incision, the midline incision with a mass closure and the midline incision with a layered closure. Polydioxanone suture was used for the fascial layer and staples for the skin to assess the suitability of polydioxanone for abdominal wound closure and to attempt to reduce the incidence of wound infection.

Patients and methods

All patients admitted under the care of T G B. and P J G between June 1987 and December 1988 undergoing elective or emergency laparotomy through a vertical abdominal incision were included in the trial. A total of 476 consecutive elective and emergency laparotomies through a vertical abdominal incision were studied of which 349 were randomized to either a lateral paramedian incision ($n = 137$) or a midline incision closed using either the mass technique ($n = 104$) or a layered closure ($n = 108$). A total of 127 patients were excluded owing to previous encroaching scars ($n = 86$), life threatening haemorrhage ($n = 20$), lack of skin staples ($n = 10$), surgeon's preference ($n = 6$) and accidental omission from the trial ($n = 5$).

The three groups were comparable for age, sex, degree of obesity, urgency of operation and seniority of the surgeon. Abnormal haematological and biochemical parameters were equally distributed within the three groups (*Table 1*). The incidence of diabetes, cardiac failure, chronic obstructive airways disease and steroid therapy was equally distributed within the three groups.

Patients eligible for the study were randomized, using a blind card system at induction of anaesthesia, to undergo either a lateral paramedian incision, or a midline incision closed by mass or layered closure (*Table 2*).

The lateral paramedian incision was made not less than two-thirds the width of the rectus sheath from the midline, the rectus muscle was dissected medially and reflected laterally as previously described[5]. The posterior sheath was incised in the same vertical plane as the anterior sheath. After the operation the wound was closed in layers using No. 1 chromic catgut to the posterior sheath with 0·5 cm bites at 2 cm intervals and No. 1 polydioxanone to the anterior rectus sheath with 0·5 cm bites at 2 cm intervals.

The midline incision was sutured with No. 1 polydioxanone using the mass technique. At least 2 cm bites at 1 cm intervals were taken for all layers excluding skin, starting at the top and the bottom of the wound so that the closure was completed at the midpoint of the wound.

The layered closure of the midline incision used No. 1 chromic catgut to the peritoneum with 0·5 cm bites at 2 cm intervals and No. 1 polydioxanone to the linea alba/rectus muscle with at least 2 cm bites at 1 cm intervals.

The length of the fascial incision was measured with a steel ruler

Table 1 *Patient details*

	Lateral paramedian	Midline mass	Midline layered
Age (years)	61	65	60
range	20–91	27–90	20–91
Sex (% male)	36	43	36
Obesity (depth cm)	3·7	3·5	3·3
range	1–8	1–8	1–8
Bilirubin (μg/l)	21(38)	10(12)	14(21)
range	4–256	3–136	4–114
Serum albumin (g/l)	36(6)	36(7)	37(6)
range	20–48	18–50	18–50
Plasma urea (mmol/l)	5(3)	5·7(4·2)	5(2·8)
range	1·3–22	1·2–34	1·3–22
Haemoglobin (g/dl)	13·1(1·7)	12·8(1·8)	12·8(1·9)
range	8·5–17·4	8–19	8–19
Malignancy (%)	30	53	39
Emergency (%)	19	31	24
Consultant (%)	23	22	25
Senior registrar (%)	27	20	21
Registrar (%)	50	58	54

Values are mean(s.e.m.)

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before closure. All remaining pieces of polydioxanone were saved in an individual labelled packet for subsequent measurement. The knots were all buried and consisted of at least five throws, two of which were locking. No tension sutures were used, drains were brought out through separate incisions, and the skin was closed with Appose® staples (Davis and Geck, Gosport, UK).

Each patient had a standard proforma completed with details of age, sex, diagnosis, operative procedure, past medical history, drug history and levels of haemoglobin, urea, bilirubin and albumin. The time to perform the incision (from incising the skin to starting the laparotomy) and to complete the closure (first stitch to the last staple), the length of the fascial incision and the length of polydioxanone used were recorded. Prophylactic antibiotics were administered to all patients and were continued for at least 48 h postoperatively. Wounds were examined daily for evidence of infection and dehiscence and the staples were removed on the 12th postoperative day Significant wound infections were defined as a discharge from the wound giving a positive culture. All wounds were reviewed at 1, 6 and 12 months when the patient was examined for incisional hernia and palpable knots and questioned about wound pain, numbness and wound discharge. Patients unable to attend were sent a questionnaire, as were all patients on completion of the study at 12 months follow-up

Results

Follow-up ranged from 6 months to 2 years and the percentage total of patients followed up was 93 per cent for the lateral paramedian incision, 89 per cent for the mass closed midline incision and 88 per cent midline incision closed in layers. Of all patients reviewed 78 per cent were at least 1 year after surgery.

There were no burst abdomens or incisional hernias in the lateral paramedian group. In the midline mass sutured group there were seven incisional hernias. Seven incisional hernias occurred in the layered closure of the midline incision of which three were complete dehiscences requiring resuture as an emergency. These differences were statistically significant ($P<0{\cdot}01$, χ^2 test) (*Table 3*).

The mean(s.d.) suture length to wound length ratio for the lateral paramedian incision and midline incision closed with mass technique or layered closure was 2·6(0·9), 5·0(1·2) and 3·7(0·8) respectively. These differences between the three groups were statistically significant ($P<0{\cdot}001$ by the Mann–Whitney *U* test) (*Table 4*). In patients with incisional hernias the median suture length to wound length ratio was 4·9 (midline mass) and 3·1 (midline layered).

The incidence of infection was 7 per cent in lateral paramedian incisions, 11 per cent in mass closure of midline incisions and 5 per cent in layered closure of midline incisions with no incidence of knot protrusion or chronic wound sinus. Two of the 11 patients with an incisional hernia not requiring emergency resuture had a wound infection (*Table 4*).

Table 2 *Distribution of conditions among randomized patients*

	Large bowel	Upper gastrointestinal tract	Miscellaneous
Lateral paramedian	45 (32)	73 (54)	19 (14)
Midline mass	50 (48)	42 (40)	12 (12)
Midline layered	52 (48)	50 (46)	6 (6)

Values in parentheses are percentages

The mean(s.e.m.) time taken to open and close the lateral paramedian incision was 22(3) (range 11–31) min as opposed to 15·5(2) (range 8–26) min for the midline incision closed in layers and 18(3) (range 10–27) min closed by the mass technique.

Early mortality less than 30 days after operation was 2 per cent in patients undergoing lateral paramedian incision, 3 per cent for those undergoing midline incision closed with mass technique and 6 per cent for those with layered closure of the midline incision of which 2 per cent had burst abdomens. The late mortality (greater than 30 days after operation) was 12 per cent, 7 per cent and 12 per cent respectively for the three incisions.

Discussion

Jenkins established the importance of a high suture length to wound length ratio in wound closure to decrease the incidence of incisional hernia[8]. Previous trials have shown the lateral paramedian incision to have a low incidence of incisional herniation[1–7]. A criticism of these studies is that good results were due to good surgical technique in obtaining a high suture length to wound length ratio.

The results of the trial reveal the lateral paramedian incision to have a significantly lower incidence of incisional hernia despite a mean suture length to wound length ratio of only 2·6 (range 1·3–6·2). In contrast, using mass closure technique for the midline incision, there was a 6·5 per cent incidence of incisional hernia with a mean suture length to wound length ratio of 5·0 (range 3·0–8·7) and when closed in layers there was a 6 per cent incidence of incisional hernia. In this latter group the suture length to wound length ratio was 3·7 (range 2·0–6·3) with over 60 per cent of patients having a suture length to wound length ratio of less than 4·0 This is due to the technical difficulty of taking 2 cm 'bites' of tissue with the peritoneum already closed and the danger of perforating or catching bowel with the suture.

These data show that the integrity of the lateral paramedian is independent of a high suture length to wound length ratio and is probably due to the 'shutter mechanism' provided by the rectus abdominus muscle[4]. An adequate suture length to wound length ratio of greater than 4·0 is generally obtained in

Table 3 *Incidence of burst abdomen and incisional hernia*

Total 349	Burst abdomen	Incisional hernia
Layered midline ($n=108$)	3 (2·5)	4 (3·5)
Mass closure ($n=104$)	0	7 (6·5)*
Lateral paramedian ($n=137$)	0	0

Values in parentheses are percentages; * $P<0{\cdot}01$ (midline layered *versus* lateral paramedian, midline mass *versus* lateral paramedian, χ^2 test)

Table 4 *Wound details*

	Suture length: wound length ratio*	Wound length (cm)	Suture length (cm)	Time in (min)	Time out (min)	Infection†
Midline layered ($n=108$)	3·7(0·8)‡	21	77	4·5	11	6 (6)
range	2·0–6·3	12–38	34–175	1–10	6–18	
Mass closure ($n=104$)	5·0(1·2)	22	109	5	13	12 (12)
range	3·0–8·7	15–32	51–180	1–10	8–19	
Lateral paramedian ($n=137$)	2·6(0·9)‡	21	55	11	11	10 (7)
range	1·3–6·2	12–36	25–118	4·5–20	5–18	

* Values are mean(s.d.); † values in parentheses are percentages; ‡ $P<0{\cdot}001$ (Mann–Whitney *U* test compared with lateral paramedian)

the mass closure but despite this the incidence of incisional hernia is the same as the layered closure, although this latter group does include three patients with a burst abdomen.

The use of polydioxanone suture in abdominal wound closure has been tested in previous trials[10–12]. In this study the short term suitability of polydioxanone for the closure of midline and lateral paramedian incisions (with the added benefit of a decreased incidence in wound sinus and knot protrusions) is confirmed[11,12]. In the midline incision the incidence of incisional hernia is similar to that of trials which employed a non-absorbable suture material. There are no studies with long term follow-up of patients with abdominal wounds closed with polydioxanone.

A continued criticism of the lateral paramedian incision is the extra operating time required. This study shows the decreased incidence of incisional hernia is not gained at the expense of a greatly prolonged operating time.

This prospective randomized trial confirms that the lateral paramedian incision is inherently strong and has a low incidence of incisional hernia, presumably owing to the shutter mechanism provided by the rectus abdominus muscle and is not dependent on a high suture length to wound length ratio. The midline incision has a significantly greater incidence of incisional hernia than the lateral paramedian incision and, in this trial, was not strengthened by mass closure. Using mass closure it was routinely possible to achieve the ideal 4:1 suture length to wound length ratio, but when the peritoneum was closed this ideal ratio was not attained in over 60 per cent of patients..

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Synthesis of collagen types I and III in reincised wounds in humans

The problem of the biochemical quantification of long term human wound healing was approached by measuring collagen synthesis in reincisions using specific radioimmunoassays for the wound fluid concentrations of the carboxyterminal propeptide of type I procollagen (PICP) and the aminoterminal propeptide of type III procollagen (PIIINP). First-day wound fluid PICP concentration after reincising a 3 week old scar was 25 times higher than the mean value in 20 reference standard incisions but scars older than 3 months did not show this difference. Wound fluid taken in subsequent days demonstrated that the initial acceleration of synthesis disappeared by the fourth day. When wound fluid PIIINP was assessed, high concentrations were found in reincisions of wounds for up to 5 months after the previous operation. The acceleration was also lost more slowly during the first postoperative week. The duration of a high rate of type I collagen synthesis compares well with studies in experimental wounds which show increased gain of strength if they are made not more than 6 weeks after previous surgery. The longer activity of the metabolism of type III collagen related antigens could reflect their function in the regulation of collagen fibril formation.

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The strength of a mature wound is due to the collagen fibres which anatomically connect the wound margins The most abundant component of this scar tissue is type I collagen. The strength of an early wound is based on a different complex mechanism, involving interactions between fibrin, fibronectin, collagen, glycosaminoglycans and wound fibroblasts[1,2]. Type I and type III procollagens contain additional propeptide extensions at both ends of the molecule[3]. During collagen deposition in the tissue, as during wound healing, enzymatic cleavage of the carboxyterminal propeptides is necessary for proper fibre formation, whereas that of the aminoterminal propeptides is not complete. Consequently, type III collagen molecules which have retained their aminoterminal propeptide extensions can often be found on the surface of collagen fibres. This partially processed form of collagen, so-called pN collagen, possibly contributes to the regulation of the fibril diameter[4].

Methods for measuring concentrations of the carboxyterminal propeptide of type I procollagen (PICP) and the aminoterminal propeptide of type III procollagen (PIIINP) in biological fluids[5,6] have made it possible to evaluate collagen synthesis in healing human wounds. Sampling contamination does not interfere with the results. Difficulties in the interpretation of the origin of soluble and insoluble collagen fractions[7] as well as the problems associated with the use of radioactive labels[8] are also avoided. Collagen synthesis begins very early as the mean second-day PICP concentration is 4·5-fold higher than found on day 1. Synthesis of both types of collagen then increases very rapidly during the first postoperative week without any sign of slowing down[9,10]

Study of collagen synthesis in human wounds for more than the first postoperative week meets with ethical and practical difficulties. Therefore, in the present study the reincisions in 12 patients were investigated at the time of reoperation 3 weeks to 25 months after previous surgery. The assumption was made that the wound fluid collected during the first day mainly reflects the previous activity without any quantitatively significant effect of the present wound. The purpose was to find out for how long collagen metabolism is accelerated in the scar tissue and whether this advantage of reincision is lost during the first postoperative week, when compared with reference standard wounds.

Patients and methods

Twelve selected patients, seven men and five women, with uncomplicated wound healing after their first operation were studied (mean age 54 years, range 24–80 years) They were operated upon electively at Oulu University Central Hospital for major gastrointestinal illness (*Table 1*). For wound infection prophylaxis, single doses of appropriate antibiotics were given intravenously at the induction of anaesthesia. All the patients had had a previous operation through the same incision 23 days to 25 months earlier, and the present operation was not performed to treat a wound complication or its sequelae. None of the patients had diabetes

Wounds of 20 patients operated on for colorectal cancer were used as reference standard wounds Although some of them had also had an incision at least 4 years earlier, it did not cause any additional variation within this group[10]. Wound fluid of these patients was collected using the same protocol as for the reincision group and the laboratory measurements were done within 6 months with the same assays. The study was approved of by the Ethical Committee of the Medical Faculty of the University of Oulu and carried out according to the provisions of the Declaration of Helsinki.

Collection of wound fluid

For collecting wound fluid, two 15 cm Silastic® (Dow Corning, Michigan, USA) silicone rubber tubings (Dow Corning medical grade tubing no 602-235, external diameter 2 mm) were left subcutaneously in the wound at the end of the operation, as previously described[9]. Samples of wound fluid, maximally 1 ml, were then drawn daily for 7 days or until discharge by puncturing the tubing. All the samples were stored at −20°C until analysed Dilutions were made in phosphate-buffered saline, pH 7·2, containing 0 04 per cent of Tween 20 (ICI Americas, Wilmington, Delaware, USA) The amount or quality of the fluid (bloody/serous) is known not to have any effect on the results[9,10]. No wound healing complications were seen in this series.

Radioimmunoassay for analysing wound fluid PICP

A new radioimmunoassay for the carboxyterminal propeptide of type I procollagen was used to measure its concentration in wound fluid (PICP)[5]. The assay is based on a polyclonal rabbit antiserum against the PICP, which is set free by bacterial collagenase digestion and purified from type I procollagen produced by primary cultures of human skin fibroblasts The radioimmunoassay procedure is briefly as follows: 0 1 ml of an antiserum dilution capable of binding about 50 per cent of the labelled antigen was incubated for 2 h at 37°C with 0·1 ml of non-labelled standard antigen or unknown sample before adding 0·1 ml

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Table 1 *Characteristics of the patients*

No.	Age (years)	Sex	Interval (months)	Present operation	Type of previous operation	Type of present operation
1	63	M	0·8	19 Feb 86	Exploration for gastric cancer	Re-exploration
2	38	F	3·1	11 May 88	Emergency colectomy for ulcerative colitis	Ileal pouch reconstruction
3	43	M	3·5	17 May 89	Emergency colectomy for ulcerative colitis	Excision of rectum with ileostomy
4	64	F	4·6	26 Apr 88	Drainage and sigmoidostomy for pelvic abscess*	Sigmoid resection and reanastomosis
5	35	M	5·1	14 Dec 87	Suture of gastric ulcer perforation	Exploration for gastric cancer
6	23	F	5·6	29 Aug 89	Emergency colectomy for ulcerative colitis	Ileal pouch reconstruction
7	24	M	6·5	21 Sep 89	Hartmann operation for traumatic perforation of colon	Sigmoid resection and reanastomosis
8	73	M	7·0	12 May 88	Hartmann operation for diverticular perforation	Sigmoid resection and reanastomosis
9	64	M	10·6	12 Aug 88	Anterior resection for rectal cancer	Exploration for recurrent cancer
10	80	F	13·5	25 Nov 85	Gastrectomy for cancer	Exploration for recurrent cancer
11	68	M	16·2	13 Feb 86	Resection for prepyloric ulcer	Gastrectomy for cancer
12	71	F	25·0	5 Oct 89	Anterior resection for rectal cancer	Enteroanastomosis for recurrent cancer

* In the first operation 10 days earlier hysterectomy was performed

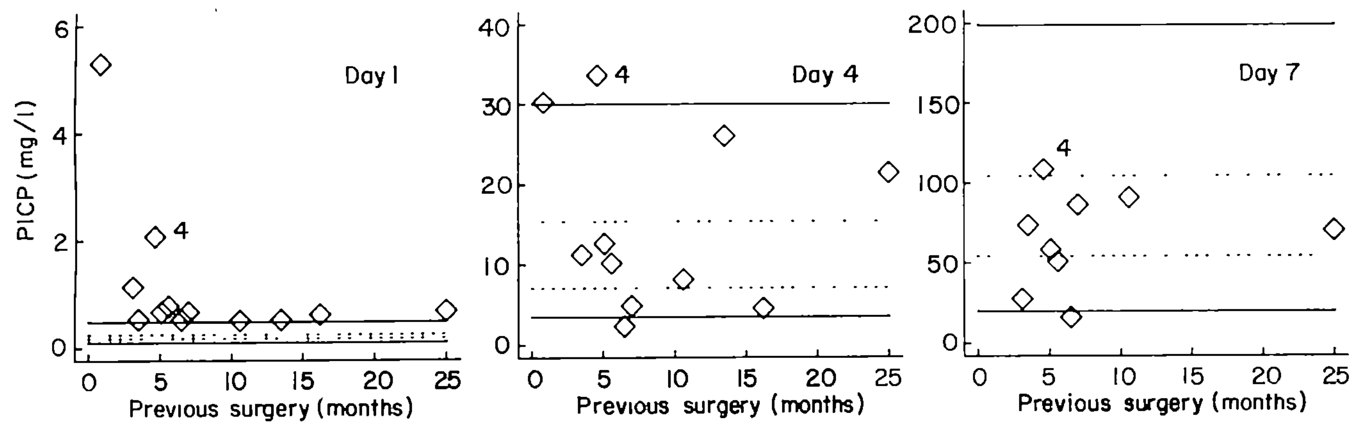

Figure 1 *The concentration of the carboxyterminal propeptide of type I procollagen (PICP) in wound fluid of reincisions as a function of the age of the previous scar. Postoperative days 1, 4 and 7 are illustrated. Maximum and minimum (continuous lines) and 95 per cent confidence limits for the mean (dotted lines) from a previous study (Haukipuro* et al., *1991, Ref. 10) are used as a reference. Note different scales 4 = Patient No. 4*

of ^{125}I-labelled PICP After a further incubation of 1 h at 37°C the free and bound antigens were separated by overnight precipitation at 4°C with a goat antiserum (second antibody) against rabbit IgG. The precipitate was collected by centrifugation for 30 min at 4°C, dissolved in 1 ml of phosphate-buffered saline and recentrifuged The radioactivity in the precipitate was then counted using LKB-Wallac Clinigamma (Pharmacia-Wallac, Turku, Finland) counter. All the samples of each patient were determined in the same run The intra-assay and inter-assay coefficients of variation were 5 per cent and 6 per cent, respectively.

Radioimmunoassay for analysing wound fluid PIIINP

The concentration of the aminoterminal propeptide of type III procollagen in wound fluid was analysed under sequential conditions using a radioimmunoassay[6] based on the human antigen (Farmos Diagnostica, Oulunsalo, Finland). It is sensitive to the authentic propeptide and a larger PIIINP related antigen, but the smaller degradation products of the propeptide are not measured. The results reflect the synthesis of type III procollagen in human wound[9,11]. The actual laboratory procedure was comparable to that of the PICP assay described above The volumes used were 0·1 ml for antiserum, 0·1 ml for standard, and 0·2 ml for samples. The intra-assay and inter-assay coefficients of variation were 4 per cent and 7 per cent, respectively.

The proportion of type III procollagen of the sum of type I and type III procollagens in the wound was calculated using the known molecular weights of PICP (M_r 100000), PIIINP (M_r 42000) and type I and III procollagens (M_r 450000). To calculate the amount of the respective procollagen the multiplication factors 4·5 and 10·7 for PICP and PIIINP, respectively, were used.

Statistical analysis

The statistical analyses and graphics were generated with Statgraphics® software (STSC, Inc., Rockville, Maryland, USA) Mann–Whitney *U* was calculated, and after *z*-transformation used to compare the proportions of type III procollagen in primary wounds and reincisions (*Figure 3*). The time to reach the minimum of the proportion was compared similarly. The confidence intervals (CI) of the differences between the medians were calculated at the 95 per cent level of significance[12]. The correlation of the proportion with the time passed from the previous operation was studied with Spearman rank correlation analysis.

Results

First-day wound fluid PICP concentrations were very high if the incision was made through a recent scar (*Figure 1*) In the patient relaparotomized 3 weeks after the previous exploration, the first-day wound fluid PICP (5·3 mg/l) was 25-fold greater than the respective average in the reference standard wounds. In primary incisions, this level is usually reached between days 3 and 4 postoperatively. However, on days 4 and 7 all the reincision patients had concentrations comparable with those in respective reference standard wounds. Patient 4 (*Table 1*) had had two recent operations for pelvic infection, probably

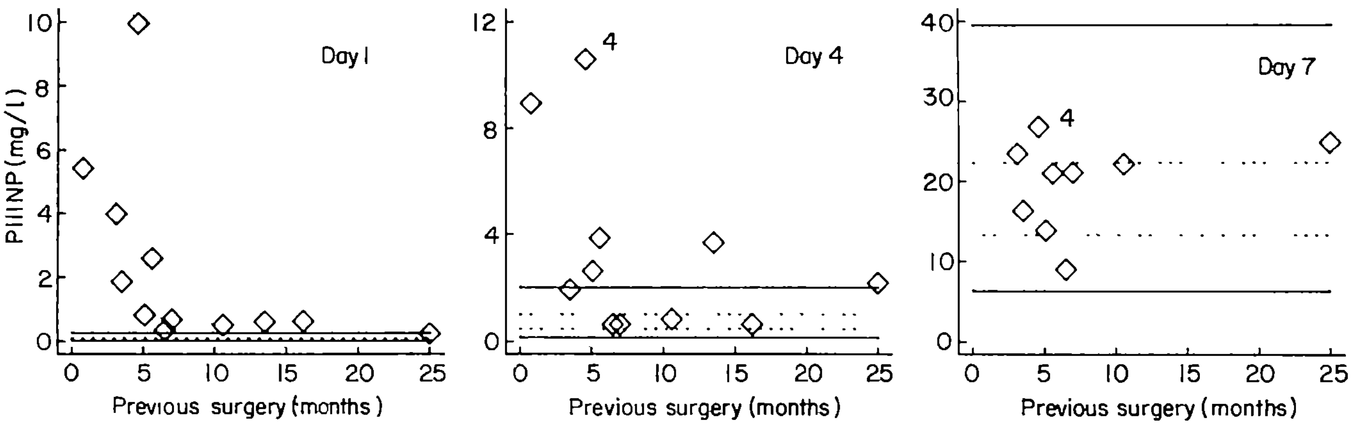

Figure 2 *The concentration of the aminoterminal propeptide of type III procollagen (PIIINP) in wound fluid of reincisions as a function of the age of the previous scar. Postoperative days 1, 4 and 7 are illustrated Maximum and minimum (continuous lines) and 95 per cent confidence limits for the mean (dotted lines) from a previous study (Haukipuro* et al., *1991, Ref 10) are used as a reference Note different scales. 4 = Patient No 4*

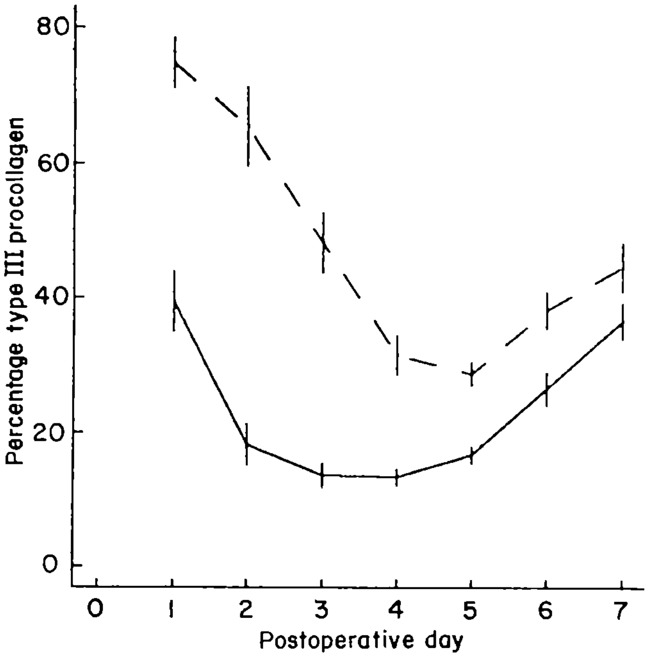

Figure 3 *The proportion (mean(s.e.m.)) of type III procollagen from the sum of type I and type III procollagen in wound fluid in primary wounds (——) of 20 patients and in reincised wounds (---) of 12 patients. The calculations are based on the molecular weights of PICP (M_r 100 000), PIIINP (M_r 42 000) and type I and III procollagens (M_r 450 000) and assuming a stoichiometric relation of a certain propeptide to its respective procollagen*

derived from complicated diverticulitis of the sigmoid colon. Her original and present wounds healed without any complication, however.

Wound fluid PIIINP followed a pattern somewhat different from that of PICP (*Figure 2*) Three weeks after previous surgery the first-day wound fluid PIIINP (5·4 mg/l) was 77-fold greater than the mean of the reference standard wounds. The effect of the previous operation on the first-day wound fluid PIIINP disappeared more slowly The concentration on day 4 continued to be high in some patients when the previous operation was within a year. Again, on day 7 the reference interval was reached. Throughout the study period the first-day wound fluid PICP and PIIINP were at least as high as the respective maximum value of the reference standard wounds. When the curves of individual reoperated patients were reviewed, lower wound PIIINP was often seen on days 2 and 3 than on day 1, especially in patients with high initial levels.

The mean proportion of type III procollagen relative to the sum of both procollagen types (III/I + III) (*Figure 3*) was higher in reoperated patients on all days, but a continuous decrease of the difference was seen during the postoperative week. On day 1, the difference between the medians of the proportions (III/I + III) was highly significant ($z = 4{\cdot}1$, $P < 0{\cdot}0001$, CI 23–51 per cent). The curves were also different, as the time to reach the minimum of the proportion was shorter in primary wounds (median 3, mean 3·5 and s.d. 1·1 days) than in the reincisions (5, 4·7 and 0·8 days) The difference between the medians is significant ($z = 2{\cdot}9$, $P < 0{\cdot}005$, CI 0–2 days) although late reincisions with their tendency to an earlier minimum of the proportion (III/I + III) approached the behaviour of primary incisions. There was also a weak negative correlation between the time which had passed from previous surgery and the proportion of type III procollagen on days 1 through 6 The correlation coefficients for the postoperative days 1, 4 and 7 were $-0{\cdot}60$ ($P = 0{\cdot}05$), $-0{\cdot}73$ ($P = 0{\cdot}02$) and $-0{\cdot}02$ ($P = 0{\cdot}96$), respectively. For clarity of presentation, the data of all reoperated patients are combined in *Figure 3*.

Three patients had collection tubes used in both their first and second operations. Two of them (Nos. 3 and 6, *Table 1*) were operated on for an acute exacerbation of ulcerative colitis. Their general condition was poor and they received steroids (methylprednisolone 80 mg/day and prednisolone 60 mg/day, respectively) at the time of their first operations. The wound fluid PICP and PIIINP in their primary wounds were mainly near or below the minimum of those of the reference standard wounds. During the time of their second operations, steroids were not given The third patient (No. 9) was one of the patients in the reference group during the time of his first operation. Patient No 2, studied only during the second operation, had received prednisolone 10 mg/day before the first, and 5 mg/day before her second operation.

Discussion

The mechanical strength of wounds involving skin and aponeurotic tissues is not attained in a linear fashion. After a certain lag the tensile strength increases rapidly for up to almost 2 months, but after 3 months the further gain is slow[13,14]. The observed duration of the increased activity of wound collagen metabolism varies with the method used. Relative collagen synthesis[8] and collagen prolyl 4-hydroxylase activity[15] return to a level normal for skin within 2–3 weeks, but absolute collagen synthesis can be activated for up to 2 months[16,17]. Finally, the diameter and morphology of the collagen fibres reach an appearance close to those of normal skin by 180 days; this also correlates with the gain of strength[14]. Subsequently, human scars between 6 months to 20 years of age maintain an unaltered level of collagen synthesis[18] During a 6-week period the amounts of type I and type III collagens increase continuously in implanted viscose cellulose sponges in the rat, a system simulating early wound healing The proportion of type III collagen decreases later from a value of about 60 per cent, seen at 1 week, to 28 per cent[19].

A scar made up to 6 weeks earlier clearly accelerates the gain of strength in a reincision[20–23]. The benefit is eliminated by a 7 mm wide excision of the wound margins[24], indicating a local origin of the stimulating factors, as opposed to earlier suggestions[25] The proposed biochemical mechanisms behind the better healing of reincisions include a different organization and cross-linking of collagen[24], a rapid synthesis and deposition of new collagen[7], a high degree of hydroxylation of collagen proline with increased synthesis[23], and an altered ratio of collagen to glycosaminoglycans[26].

In the present study, the first-day wound fluid PICP remained at least at the upper limit of the reference standard wounds (*Figure 1*). The initial great difference between the patients with a recent scar and the reference group disappeared by day 4. Thus, the reincision rapidly lost the acceleration of the synthesis provided by the previous wounding and the maximum synthesis never exceeded that of the reference. This suggests that the real maximum of the synthetic rate cannot be much higher The high rate of type I collagen synthesis for up to 3 weeks or more compares well with tensile strength measurements of reincised wounds[21,22]. Though reincisions rapidly lost their advantage, the first 4 days may still be critical from the point of view of the mechanical strength. No single factor is responsible for the tissue strength during early wound healing, and it is now known that several receptors, capable of mediating interactions between cells and extracellular matrix, exist[27]. Thus increased numbers of fibroblasts, and larger amounts of fibronectin and glycosaminoglycans, able to co-operate with collagens, can have a cumulative effect on tissue strength.

The metabolism of the PIIINP antigen is different from that of PICP. Its first-day concentration decreases more slowly as a function of the age of the scar, though statistical inferences are difficult. On the other hand, some reincisions still have increased amounts of PIIINP by day 4 (*Figure 2*). This is also reflected in the higher proportions of type III procollagen during the first days. The gradual change towards the reference group is reflected in a decreasing overall proportion of type III procollagen and its earlier minimum in reincisions through older scars. In other words, late reincisions tend to behave like primary wounds.

Most of the PIIINP antigen in wound fluid is equal in size to the authentic aminopropeptide as set free during synthesis[9,11] The presence of so high a proportion of type III procollagen (*Figure 3*) is surprising but could possibly be explained by its participation in the early achievement of the strength[1,2] Comparable amounts can be found in sponge implants in the rat[19] An active metabolism of type III procollagen even in 5 month old scars may indicate its function in regulating collagen fibril diameter, which is still changing at this time[14]. It is not known if differences exist in the tissue elimination rates of the aminoterminal and carboxyterminal propeptides as such.

A minor part of the wound fluid PIIINP is due to an antigen form larger than the authentic propeptide[11]. There is some evidence to support the view that this antigen is simply an aggregated form of the aminopropeptide and thus also reflects synthesis[28]. A transglutaminase reaction at glutamine residue No 14 in the type III aminopropeptide could allow for the aggregation of PIIINP or, primarily, the attachment of the aminoterminal part of procollagen or pN collagen to other matrix components for greater stability[29]. However, the decreasing wound fluid PIIINP as opposed to the increasing PICP levels during days 1, 2 and even 3 in the patients studied here do not fit well with the supposed induction of collagen synthesis Peak transglutaminase activities are also found later, on postoperative days 3 to 5 in the rat[30]. Turnover of tissue pN collagen as a partial source of the PIIINP antigenicity in the wound fluid is possible, demonstrating susceptibility of this form of collagen. In every case, the relative amount of type III pN collagen, which is only situated on the surface of the fibrils, is limited[31,32]. Recently, characteristics of type I pN collagen *in vitro* were studied in detail[33]. Increased proportions of type I pN collagen led to greater solubility of collagen and sheets rather than fibrils were formed. This is in agreement with the location of type I pN collagen only on the surface of thin fibrils *in vivo*[32].

In summary, in uncomplicated wound healing the increase in type I collagen synthesis is quantitatively important for less than 3 months, though the basal synthetic rate is reached slowly. The acceleration of synthesis provided by the previous wounding seems to be lost already after 4 days of healing. The metabolism of type III collagen can be active in 5 month old scars. From the clinical point of view, the advantage of the previous incision for repeated healing is probably lost within a few months.

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Autologous transfusion: an alternative to transfusion with banked blood during surgery for cancer

Autologous blood transfusion in surgery for cancer has been avoided because of the metastatic potential of reinfused malignant cells. This study determined whether viable tumour cells remain in the red cell concentrate after separation and whether blood transfusion filters remove these tumour cells before reinfusion. Units of banked blood were inoculated with tumour cell lines: breast cancer SKBr3; colon cancer COLO 320; lymphoma Daudi; erythroleukaemia K562. After processing with the Cell Saver®, aliquots of the red cell concentrate and waste saline wash were examined for tumour cells and cultured. Tumour cells from all four cell lines were identified in the red cell concentrate but not in the waste saline wash. All the cell lines except Daudi grew from the red cell concentrate. Experiments on two of the cell lines (SKBr3 and COLO 320) were performed in which the red cell concentrate was either unfiltered (control) or filtered with SQ40S blood transfusion filter or RC100 leucocyte depletion filter. Both cell lines were present in the control samples and after filtration with SQ40S filters, and cells from these samples grew normally in culture. No tumour cells were evident after filtration with the RC100 filters and no growth of either cell line was found after 1 week in culture. The Cell Saver in combination with RC100 filters may be suitable for use during the surgical treatment of malignant disease.

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Perioperative transfusion with banked blood may worsen the prognosis in patients undergoing surgery for cancer[1]. That the association stems simply from the increased transfusion requirements of patients with lesions which have a poor prognosis appears refuted[1]. Other reasons to avoid the use of banked blood include the possibility of transmission of infections such as human immunodeficiency virus or non-A non-B hepatitis, and economic considerations.

Perioperative transfusion with autologous blood utilizing a Cell Saver® (Haemonetics Corporation, Leeds, UK) may be an alternative to the use of banked blood. The device harvests blood from the operative field, washes and centrifuges the red cells in heparinized saline, producing a red cell concentrate and a waste saline wash. White blood cells, platelets and other debris are normally discarded in this component. The device has been widely used in surgery for cardiovascular[2] and orthopaedic disease[3] and in trauma[4]. It has not been fully assessed in the surgical treatment of malignant disease due to concern that tumour cells from the operative field may be reinfused into the patient. One study showed that isotopically labelled tumour cells were detected mainly within the red cell concentrate after processing with the Cell Saver[5].

The aims of this study were: (1) to determine whether viable tumour cells could survive processing with the Cell Saver and whether they remained within the red cell concentrate or were discarded in the waste saline wash; and (2) to determine whether blood transfusion filters could remove tumour cells which became incorporated in the red cell concentrate.

Materials and methods

Four malignant cell lines were chosen for study because of their different physical characteristics and availability in the laboratory: SKBr3 (breast carcinoma, monolayer, 30 μm diameter), COLO 320 (colonic carcinoma, suspension with some clumping into aggregates, 18 μm diameter), Daudi (Burkitt's lymphoma, single cell suspension, 12 μm diameter), K562 (erythroleukaemia, single cell suspension, 25 μm diameter) Established malignant cell lines were cultured in either RPMI 1640 medium or Dulbecco's Modified Eagle's Medium (DMEM) supplemented with 10 per cent fetal calf serum (FCS), 2-mercaptoethanol 5 mmol/l, amphotericin 2·5 μg/ml, gentamicin 160 μg/ml, MEM non-essential amino acids (100 × concentration) 1 ml/100 ml. All media and additives were purchased from Gibco Ltd., Paisley, UK. Cultures were incubated at 37°C in an atmosphere of 5 per cent CO_2/ 95 per cent O_2 Monolayer cultures (SKBr3) were harvested for passage with 0·25 per cent trypsin in Hank's Balanced Salt Solution (HBSS, Gibco Ltd) All cell lines were washed before passage in HBSS and resuspended in appropriate media. Cell viability was assessed by the trypan blue exclusion method using 180 μl trypan blue (15 mg/ml) and 20 μl cell suspension Viable, unstained cells were counted on a modified Nebauer counting chamber and percentage viability calculated

Experiments on cell lines

Whole human blood from the blood bank which was excess to requirements and at its expiry date was used in the study. Following harvesting and assessment of viability by trypan blue exclusion, each of the individual cell lines was inoculated in duplicate into units of whole blood The number of cells inoculated per unit was 40×10^6 for SKBr3 and Daudi, 30×10^6 for K562 and 25×10^6 for COLO 320. Following incubation and thorough mixing, each unit of blood was processed separately using a Haemonetics Haemolyte Cell Saver in its normal operating mode to produce a red cell concentrate and waste saline wash.

The red cell concentrate and saline wash were examined separately for tumour cells and cultured in appropriate media. The waste saline wash was mixed thoroughly and a 50 ml aliquot spun in a centrifuge at 500*g* for 10 min to produce a pellet The pellet was resuspended in 1 ml of complete media and examined microscopically for tumour cells and cultured. The red cell concentrate was mixed and a 50 ml aliquot was centrifuged on a Lymphoprep™ (Nycomed, Torshov, Norway) density gradient[6]. Previous (unpublished) work has been performed in our laboratory in which the separate components of the gradient were

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Table 1 *The number of tumour cells identified in the red cell concentrate (RCC) and waste saline wash (SW) after Lymphoprep separation of the RCC and culture of both components for 1 week*

	Cell number (× 10^6 per ml)	
Cell line	After Lymphoprep	After culture
SKBr3		
RCC	0·9	5·7
SW	–	1·0
COLO 320		
RCC	0·7	4·8
SW	–	–
K562		
RCC	0·5	4·5
SW	–	1·0
Daudi		
RCC	0·7	–
SW	–	–

RCC, red cell concentrate, SW, saline wash

assessed for the presence of viable tumour cells. Only the 'interface' layer between HBSS and Lymphoprep was found to contain these cells and therefore this layer was harvested, examined for malignant cells and cultured as above.

Experiments using filters

SKBr3 and COLO 320 cell lines were studied because of their cell size, growth characteristics and relevance to the clinical situation. An inoculum of 25 × 10^6 cells COLO 320 (as previously) or 32 × 10^6 SKBr3 (20 per cent reduction from previously, necessitated by a fixed cell yield and increased sample size) was added to units of banked blood. These samples were processed by the Cell Saver in its normal operating mode and the red cell concentrate collected. This fraction was not filtered (control) or filtered using one of two transfusion filters SQ40S blood transfusion filter of fixed pore aperture of 40 μm and leucocyte depletion filter RC100 which acts by membrane adsorption of charged particles (both filters, Pall Biomedical Ltd., Portsmouth, UK). Units of blood were filtered over a period of 1 h and collected in a sterile container. After preparation a 50 ml aliquot of each filtrate was separated on a Lymphoprep density gradient and the 'interface' layer collected, examined and cultured as above

Results

Experiments on cell lines

Following Lymphoprep separation of the red cell concentrate abundant tumour cells from each of the four lines could be seen in each sample of concentrate. When cultured in appropriate media a growth of each of the cell lines, except Daudi, was apparent after 24 h. These three lines continued to grow normally and after passage at 1 week. No growth was observed from the Daudi cell line.

Microscopy of the waste saline wash revealed no tumour cells. After culture for 72 h a scanty growth of SKBr3 and K562 only was apparent (*Table 1*).

Experiments using filters

Following Lymphoprep separation abundant tumour cells were demonstrated for both cell lines used in the unfiltered (control) and SQ40S filtered samples. No tumour cells were visible after filtration with the RC100 leucocyte depletion filter. After culture for 1 week, confluent growth was achieved for both cell lines in the unfiltered and SQ40S filtered samples but no growth occurred in the RC100 filtered samples. The cultured cells were successfully harvested, passaged and continued to grow normally in cell culture (*Table 2*). These cells were morphologically identical to those of the initial inoculum and survived extended passage.

Discussion

Four cancer cell lines with different physical characteristics all remain mainly within the red cell concentrate after processing with the Cell Saver. Three of these cell lines remained viable, as demonstrated by their growth and successful passage at 1 week. No tumour cells could be demonstrated microscopically within the waste saline wash but a scanty growth was obtained from two of the lines. Occasional tumour cells must therefore enter this component.

Filtration using the SQ40S standard blood transfusion filter did not remove tumour cells from the red cell concentrate. The RC100 leucocyte depletion filter effectively removed all tumour cells from the red cell concentrate and no growth occurred during the subsequent culture.

Dale *et al.*[5] labelled tumour cells with chromium-51 and demonstrated that most of the activity was found within the red cell concentrate after processing with the Cell Saver. The blood was not examined for tumour cells and there was no attempt to assess viability. Their results are in agreement with these findings.

The cell lines used in these experiments are particularly robust and may be expected to survive processing to a greater extent than disaggregated cells from an operative field involving a tumour. Banked blood, as used in these studies, provides a particularly hostile environment by comparison with fresh blood. This may be the explanation why the Daudi line failed to survive in the first series of experiments. Many tumour cells harvested at operation may not survive passage through the Cell Saver but a proportion of viable cells will be reinfused into the patient's circulation if the blood is unfiltered. Tumour cells can be demonstrated within the circulation during the surgical treatment of abdominal malignancies[7,8] Their significance is, at present, unknown. Patients' cellular antitumour immune responses are impaired in the immediate postoperative period[9] and clearly adding an additional burden of viable tumour cells to the circulation may be inadvisable.

Filtration of processed blood using RC100 filters may be a reasonable option since tumour cells were completely removed in the studies using this device. The mechanism of action, by the adsorption of charged particles, should prove equally effective on disaggregated tumour cells which are harvested with blood from the operative field. The filters, however, constrain the use of the instrument; transfusion through the filter is limited to a maximum rate of 1 unit of blood/h and the use of pressure infusors is contraindicated.

The resection of most small abdominal cancers may be accomplished without recourse to the use of banked blood The potential use of the Cell Saver and RC100 filters may aid the surgical treatment of large fixed tumours, i.e. those malignancies in which the cancer may be breached during operation. Such patients may have a significant total blood loss and this is not usually at a rate which would preclude the use of the Cell Saver in combination with the RC100 filters.

Transfusion with banked blood presently costs 170 pounds sterling for 2 units In comparison the plastic ware and RC100

Table 2 *The number of tumour cells identified after Lymphoprep separation of the red cell concentrate (RCC) and after culture for 1 week The RCC was treated by either no filtration (control) or filtration with SQ40S blood transfusion filters or RC100 leucocyte depletion filters*

	Cell number (× 10^6 per ml)	
Cell line	After Lymphoprep	After culture
SKBr3		
Control	0·7	5·5
SQ40S	0·2	4·2
RC100	0	0
COLO 320		
Control	0·8	5·0
SQ40S	1·0	4·6
RC100	0	0

SQ40S, transfusion filter, fixed pore size 40 μm; RC100, leucocyte depletion filter filters for a 2-unit autologous transfusion would cost 70 pounds sterling (assuming the device is already on site). Thus the cost of a modest transfusion is less than 50 per cent of the cost of banked blood. As transfusion requirements increase the relative costs of autologous transfusion decrease further, since the plastic ware for the Cell Saver is independent of the amount of blood processed.

In conclusion, the use of the Cell Saver in isolation during surgery for malignant disease is not recommended because of the potential danger of reinfusion of viable malignant cells. In combination with RC100 filters, however, the system would seem to be without quantifiable hazard. It may therefore be of clinical benefit to the patient as well as being economically sound.

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Severe late postsplenectomy infection

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In all, 1490 patients underwent splenectomy in Western Australia between 1971 and 1983, giving 7825 person years exposure. Thirty-three patients developed severe late postsplenectomy infection (septicaemia, meningitis or pneumococcal pneumonia requiring hospitalization) and three developed overwhelming postsplenectomy infection. The incidence and mortality rates of severe late postsplenectomy infection were 0·42 and 0·08 per 100 person years exposure respectively and for overwhelming postsplenectomy infection the incidence and mortality rates were 0·04 per 100 person years exposure. There were 628 splenectomies after trauma, giving 3922 person years exposure. Eight patients developed severe late postsplenectomy infection of whom one had overwhelming postsplenectomy infection. Following trauma, the incidence of severe late postsplenectomy infection was 0·21 per 100 person years exposure, with the incidence and mortality rates of overwhelming postsplenectomy infection being 0·03 per 100 person years exposure. Patients undergoing splenectomy have a 12·6-fold increased risk of developing late septicaemia compared with the general population. Splenectomy following trauma gives an 8·6-fold increased risk of late septicaemia. The majority of severe late postsplenectomy infections did not occur within the first 2 years and 42 per cent of severe late postsplenectomy infections occurred >5 years after splenectomy. The low incidence of severe late postsplenectomy infection and overwhelming postsplenectomy infection makes statistical evaluation of the effectiveness of prophylactic antibiotics, vaccination and splenic repair most difficult.

In 1919 Morris and Bullock[1] noted the importance of the spleen in resistance to infection and found an increased mortality in splenectomized rats inoculated with the bacillus of rat plague In 1952, King and Shumacker[2] reported the severe, often fatal, septic episodes in children after splenectomy. The first report in adults was by Whitaker[3] in 1969.

There is an increasing awareness of the risk of severe late postsplenectomy infection but the extent of this risk is not well defined. The duration of a patient's exposure to potential severe late infection following splenectomy has not been taken into account in population studies. This study was conducted to establish the incidence and mortality of severe late postsplenectomy infection in Western Australia.

Patients and methods

Definitions

The infections selected were. (1) septicaemia, as this is recognized to be the most severe infection occurring in the asplenic individual[4], (2) meningitis, to determine whether asplenic individuals are more prone to severe infections outside the vascular compartment, and (3) pneumococcal pneumonia, to determine the susceptibility to pneumococcal infections *per se*, compared with those associated with septicaemia. If patients with meningitis or pneumonia had associated septicaemia, they were placed in the septicaemia category. Severe late postsplenectomy infections were those requiring a separate subsequent hospital admission to that for splenectomy.

The term 'overwhelming postsplenectomy infection' describes the particularly fulminant form of septicaemia occurring after splenectomy, which is the most severe of all postsplenectomy infections[5] It has a rapid onset and progression, often to death within 48 h, despite intensive therapy

Study population

Western Australia has a highly stable population[6], isolated by large distances from the remainder of the continent The mean annual emigration rate from Western Australia during the study period was 1·57 per cent of its mean population of 1·17 million

The study population was patients who had undergone splenectomy in Western Australia hospitals between January 1971 and December 1983. Using the Western Australian Hospital Morbidity System of the Health Department of Western Australia and record linkage programmes (unpublished data), those patients who had undergone splenectomy and had subsequently died or required a separate hospital admission for meningitis, pneumococcal pneumonia or septicaemia were identified and their hospital records reviewed The period from 1971 to 1983 was selected for analysis to maximize the detection rate of severe late postsplenectomy infection by minimizing the effect of prophylactic antibiotic therapy (rarely prescribed before 1980) and of pneumococcal vaccination (not available in Western Australia until 1980 and not routinely used until 1982)

'Person years exposure' after splenectomy were calculated from the date of splenectomy until December 1983, or until death if earlier, using the Man Years Calculation Programme of the Department of Medicine The incidence and mortality rates of meningitis, pneumococcal pneumonia, septicaemia and overwhelming postsplenectomy infection were calculated according to person years exposure and were standardized for age using the method of direct standardization and the Western Australian population, 1981–1983, as standard weights (unpublished data).

The relative risk of developing infection following splenectomy was compared with the rate in the Western Australian population. The number of expected cases was determined as the sum of the products of the age-specific hospital admission rates for the relevant infections in the general population times the number of person years exposure contributed by that age group The relative risk of infection was the ratio of the observed rates in the splenectomized cohort to the expected rates defined above In this way a cohort analysis of the risk of infection as a function of years following splenectomy was defined Statistical significance was calculated utilizing 95% confidence intervals

Categorization of splenectomy

The indication for splenectomy was determined as follows. category I, following external trauma, category II, during surgery for malignant

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Table 1 *Incidence and mortality of severe late postsplenectomy infections in Western Australia 1971–1983*

	Incidence of infection					
Category	Meningitis	Pneumococcal pneumonia	Septicaemia	Overwhelming postsplenectomy infection	All severe infections	Mortality*
I Trauma, $n=628$ 3855 patient years	–	0·08(0·01) [3]	0·13(0·01) [5]	0·03(0·01) [1]	0·21(0·01) [8]	0·03(0·01) [1]
II Malignant, $n=142$ 967 patient years	0·10(0·02) [1]	0·10(0·02) [1]	0·10(0·02) [1]	–	0·31(0·02) [3]	–
III Non-malignant, $n=231$ 374 patients years	–	–	1·60(0·53) [6]	–	1·60(0·53) [6]	0·53(0·01) [2]
IV Haematological, $n=443$ 2385 patients years	0·08(0·01) [2]	0·17(0·01) [4]	0·42(0·02) [10]	0·08(0·01) [2]	0·67(0·01) [16]	0·13(0·01) [3]
Overall $n=1490$ 7825 patient years	0·04(0·005) [3]	0·10(0·01) [8]	0·28(0·01) [22]	0·04(0·005) [3]	0·42(0·01) [33]	0·08(0·01) [6]

Age standardized rates per 100 person years exposure (95% confidence intervals) Numbers of patients infected are shown in square brackets * All late postsplenectomy infectious deaths were from septicaemia

conditions; category III, surgery for non-malignant conditions; category IV, haematological or lymphoproliferative disorders; and category V, those whose splenectomy could not be classified into the other four categories

Results

During the 13-year study period, 1490 patients underwent splenectomy in Western Australia; 903 males and 587 females contributed 7825 person years exposure with a mean of 5·25 years. Included in these figures were 183 children (under 15 years of age) contributing 779 person years exposure. The numbers undergoing splenectomy and the person years exposure contributed by each category are listed in *Table 1*. Forty-six patients were in category V, contributing 244 person years exposure.

The age of patients ranged from 19 months to 84 years, with a median of 31 years for both males and females. In those undergoing splenectomy for trauma there was a peak incidence in the 15–29-year age group. There were 323 splenectomies performed in this subgroup accounting for 51·4 per cent of all splenectomies and of these, 77·7 per cent were males.

The age-standardized rate of splenectomy per 100 000 population in Western Australia between 1971 and 1983 was 11·7 (95% confidence intervals 10·6–12·6) for males and 7·6 (95% confidence intervals 6·6–8·6) for females During the review period the splenectomy rate in children fell from 5·2 (95% confidence intervals 3·8–6·8) in 1971–1974 to 2·4 (95% confidence intervals 1·31–3·6) in 1981–1983 which may reflect altered indications and increased conservative management of splenic trauma.

Of the 1490 splenectomized patients, 33 (2·2 per cent) developed severe late postsplenectomy infection: three (0·2 per cent) with meningitis, eight (0·5 per cent) with pneumococcal pneumonia and 22 (1·5 per cent) with septicaemia of whom three (0·2 per cent) had overwhelming postsplenectomy infection. Of the 22 with septicaemia, five (0·8 per cent) occurred after splenectomy for trauma, one (0·7 per cent) after splenectomy during surgery for malignant disease, six (2·6 per cent) after splenectomy during surgery for non-malignant disease and ten (2·3 per cent) after splenectomy for haematological or lymphoproliferative disorders (*Table 1*). None of the patients in the unclassified category V developed severe late postsplenectomy infection.

The incidence of severe late postsplenectomy infection and overwhelming postsplenectomy infection were age-standardized per 100 person years exposure. The overall incidence rate of severe late postsplenectomy infection was 0·42, of which meningitis accounted for 0·04, pneumococcal pneumonia 0·10 and septicaemia 0·28 per 100 person years exposure (*Table 1*) In the paediatric population only one patient with severe late postsplenectomy infection was found, a case of overwhelming postsplenectomy infection, giving an incidence and mortality rate of 0·13 per 100 person years exposure. After splenectomy for trauma, the incidence of severe late postsplenectomy infection was lower than for the other splenectomy categories, being 0·21 per 100 person years exposure, with an incidence of septicaemia of 0·13 and of overwhelming postsplenectomy infection of 0·03 per 100 person years exposure

Six patients died from septicaemia and three had overwhelming postsplenectomy infection. All three with overwhelming postsplenectomy infection had had a prodromal illness (in two for >48 h), one had undergone splenectomy for trauma and two had undergone splenectomy for idiopathic thrombocytopaenic purpura. The mortality from late postsplenectomy septicaemia was 0·08 per 100 person years exposure with a mortality rate from overwhelming postsplenectomy infection after splenectomy for trauma of 0·03 per 100 person years exposure (*Table 1*).

The increased risk of developing septicaemia after splenectomy was 12·6 times that of an age-matched non-splenectomized cohort (*Table 2*). Of the six patients developing septicaemia after splenectomy for non-malignant disease, two had chronic liver disease and three had developed malignant conditions since their splenectomy (two adenocarcinoma and one non-Hodgkin's lymphoma). When the results were corrected for the subsequent change in diagnosis, the increased risk of developing septicaemia was 8·6-fold after splenectomy for trauma, 7·1-fold for malignant disease, 15·0-fold for non-malignant disease and 24·4-fold after splenectomy for haematological or lymphoproliferative disorders.

The death rate from overwhelming postsplenectomy infection was more than 300 times that expected from septicaemia in the age-standardized population but there was no increased frequency of meningitis or pneumococcal pneumonia.

Bacteriology

In the 22 patients with a clinical diagnosis of septicaemia, 19 positive blood cultures were obtained, *Streptococcus*

Table 2 *Increased risk of developing septicaemia after splenectomy compared with age-specific rates for Western Australian population*

Category	Observed	Expected	O/E-Risk	Corrected figures*	
				Observed	O/E-Risk
I Trauma	5	0·58	8·6(7·5)	5	8·6
II Malignant	1	0·42	2·4(4·8)	3	7·1
III Non-malignant	6*	0·20	30·1(24·0)	3	15·0
IV Haematological	10	0·45	22·1(13·7)	11	24·4
Overall	22	1·75	12·6(5·3)	22	12·6

Values in parentheses are ±95% confidence intervals. * Corrected figures for subsequent change in diagnostic categories after splenectomy: two patients in category III subsequently developed adenocarcinoma and one developed non-Hodgkin's lymphoma before their episode of septicaemia. O, observed; E, expected

Table 3 *Bacteriology of postsplenectomy septicaemia*

Organism	No. of patients
Streptococcus pneumoniae	6 (32)
Escherichia coli	5 (26)
Klebsiella species	2 (11)
Proteus species	2 (11)
Haemophilus species	1 (5)
Serratia species	1 (5)
Streptococcus viridans	1 (5)
Gram-negative rod, not identified	1 (5)
Total	19

Values in parentheses are percentages

pneumoniae (pneumococcus) being the most common organism (32 per cent of cases) (*Table 3*). Encapsulated bacteria (including *Escherichia coli* which possess a microcapsule of acidic polysaccharide) were responsible for 79 per cent of positive blood cultures.

Of the 33 severe late postsplenectomy infections, 12 (36 per cent) occurred within 24 months of splenectomy, seven (21 per cent) between 2 and 5 years after splenectomy and 14 (42 per cent) >5 years after splenectomy. There was no correlation between the severity of septic episode and interval since splenectomy.

None of the patients developing severe late postsplenectomy infection had received antibiotic prophylaxis or pneumococcal vaccine. Two separate pneumococcal infections occurred in a patient with non-Hodgkin's lymphoma despite vaccination with pneumococcal vaccine.

Discussion

In this study no significant increase in incidence of pneumococcal pneumonia or meningitis was found after splenectomy but all splenectomized patients had an increased risk of developing late septicaemia. Splenectomy gave a 12·6-fold (95% confidence intervals 7·3–17·9) increased risk of developing septicaemia when compared with the general population. The incidence and mortality rates of severe late postsplenectomy infection were 0·42 and 0·08 per 100 person years exposure respectively.

The reported incidence of severe late postsplenectomy infection and overwhelming postsplenectomy infection varies considerably in the literature (*Table 4*) owing to differences in referral patterns and surgical practice (e.g different percentages of children and trauma). One study[7] included infections such as pneumonia, urinary tract infections and subphrenic abscesses in the perioperative period. These were complications of the trauma sustained, treatment given and operative procedure rather than the asplenic state. Differences exist as to what constitutes late postsplenectomy infection: miliary tuberculosis[8], osteomyelitis, rheumatic fever, respiratory tract infections[9], peritonitis[10], late wound infections[11], intra-abdominal abscesses, Herpes zoster[12] and pyrexia of unknown origin[13] have been included. Others[14–17] give insufficient detail to allow categorization of the infections. Some studies[10,14,15,18] evaluated the mortality from severe late postsplenectomy infection but not its incidence. A few[13,15] did not differentiate between indications for splenectomy when calculating rates for severe late postsplenectomy infection.

Among studies examining late infection after splenectomy for trauma (*Table 5*), some[14,16,19] did not exclude iatrogenic trauma or splenectomy incidental to the surgical procedure. Because the larger studies[4,16] have derived incidence rates from other published reports, mostly single centre studies, their results may be biased.

Some studies document the person years exposure (*Table 6*), enabling the calculation of the incidence of severe late postsplenectomy infection as an expression of time exposure. Several gave insufficient detail to allow calculation of the incidence after splenectomy following trauma[10,14,15,19].

The indication for splenectomy affected the incidence of severe late postsplenectomy infection and splenectomy for haematological or lymphoproliferative disorders was associated with a higher incidence of severe late postsplenectomy infection than that after trauma, in keeping with other studies[4,7,16,17,19].

After splenectomy for trauma there was an 8·6-fold increased risk of developing late septicaemia but the incidence of severe late postsplenectomy infection was low at 0·21 per 100 person years exposure, similar to that found by Malangoni *et al.*[20] There may be a partial protective effect from splenosis, owing to growth of self-implanted remnants of the traumatized spleen but splenosis does not guarantee protection from overwhelming postsplenectomy infection[21].

In this study, after splenectomy for trauma, the mortality from severe late postsplenectomy infection was 0·03 per 100 person years exposure, a crude incidence of 0·2 per cent. There are many case reports of severe late postsplenectomy infection or overwhelming postsplenectomy infection where numbers have not been evaluated[22]. Excluding these, only 23 deaths have been reported from severe late postsplenectomy infection in 4221 splenectomies following trauma, a collective mortality rate of only 0·5 per cent despite the bias from the high proportion (51 per cent) of children reviewed (*Table 5*).

In those studies documenting person years exposure after splenectomy for trauma (*Table 6*), only three cases of overwhelming postsplenectomy infection have been reported in 7246 person years exposure, an incidence rate of 0·041 per 100 person years exposure. Following any form of splenectomy, only ten cases of overwhelming postsplenectomy infection have been reported, an incidence rate of 0·058 per 100 person years exposure.

Increased surgical awareness of overwhelming postsplenectomy infection is leading to modifications of surgical practice. Surgeons attempt repair of iatrogenic splenic injuries and in

Table 4 *Summary of studies on late postsplenectomy infection*

				Sepsis			
First author*	No of patients	Children (%)	Trauma† (%)	Definition‡	Incidence (%)	Mortality rate (%)	OPSI‡ (%)
Lowdon[8] (P)	1118	17	21	All	8·0	2·0	0·2
Kiesewetter[9]	205	100	10	All	6·3§	1·5§	1·0
Singer[4]	2795	57	25	SMP	4·3	2·5	ns
O'Neal[14]	256	Nil	50	S	ns	2·7	ns
Schwartz[7]	193	ns	25	All	26·9	0·5	0·5
Standage[15]	175	Nil	23	LH	ns	11·4	ns
Ellison[16] (M)	5579**	75	35††	ns	3·1**	1·7**	ns
Pedersen[19] (P)	384	100	53	SM	5·5	1·6	ns
Malangoni[20]	140	Nil	100	SMP	2·1	0	0
Carlstedt[13]	133	ns	26	LH	12·8	0	0
Chaikof[10]	637	81	15	LH	ns	5·3	0·6
Pate[32]	316	ns	50	S	ns	0·3	0·3
Sekikawa[11]	242	ns	100	LH	2·5	0	0
Vichard[33]	228	Nil	100	All	12·0‡‡	1·7§§	0
Green[12]	144	Nil	100	LH	9·7	0·7	0·7‡
Green[34]	18	100	100	LH	11·1	0	5·5
DiCataldo[18]	148	ns	47	S	ns	0	0
Selby[17]	131	ns	ns	S	4·6	1·5	0
Present study (P)	1490	12	42	SMP	2·2	0·4	0·2

* Superscript number is the reference; all studies from single centres except M, multiple review, P, population study † Trauma excludes iatrogenic trauma or incidental splenectomy unless indicated. ‡ Definition of sepsis. All, all infections, LH, sepsis requiring late hospitalization, M, meningitis, P, pneumonia; S, septicaemia; OPSI, overwhelming postsplenectomy infection, patient numbers adjusted to conform to accepted definition[5], ns, not stated. § Adjusted to exclude infections within 1 month of splenectomy ** Includes data from Singer[4] and O'Neal[14] †† Includes incidental or iatrogenic splenectomy ‡‡ Mostly viral infections. §§ All deaths from sepsis occurred in patients with multiple trauma, the time interval following splenectomy is not specified. *** Combined total corrected for Ellison's[16] inclusion of data from Singer[4] and O'Neal[14] ††† Corrected to exclude studies where sepsis type not stated. Some symbols appear only in *Tables 5* or *6*

Table 5 *Summary of studies on late infection after splenectomy for trauma†*

			Sepsis			
First author*	No of patients	Children (%)	Definition‡	Incidence (%)	Mortality rate (%)	OPSI‡ (%)
Lowdon[8] (P)	287	34	SMP	0·7	0·3	0
Singer[4]	688	56	SMP	1·4	0·6	4
O'Neal[14]	128†	0	S	ns	0	0
Schwartz[7]	48	ns	All	20·8	0	0
Ellison[16] (M)	1954**††	87	ns	1·4**††	0·8**††	ns
Pedersen[19] (P)	204††	100	SM	2·5††	0·5††	ns
Malangoni[20]	140	0	SMP	2·1	0	0
Chaikof[10]	96	20	LH	ns	0	0
Pate[32]	158	ns	S	ns	0	0
Sekikawa[11]	242	ns	LH	2·5	0	0
Vichard[33]	228	0	All	12·0‡‡	1·7§§	0
Green[12]	144	0	LH	9·7	0·7	1‡
Green[34]	18	100	LH	11·1	0	1
Selby[17]	74	ns	S	0	0	0
Present study (P)	628	15	SMP	1·3	0·2	1
Combined***	4221	51			0·5	7

See footnotes to *Table 4*

some diseases, especially Hodgkin's lyphoma, the frequency of elective splenectomy has been reduced.

After trauma attempts should be made at splenic repair in stable patients but should not otherwise prolong the operation Splenic autotransplantation is not fully evaluated and protection is not guaranteed[23,24]. It carries the risk of graft necrosis with abscess formation and may result in an increase in adhesive bowel obstruction[25].

Asplenic patients should be considered to have a life-long risk of developing severe late postsplenectomy infection,

Table 6 *Summary of studies on late postsplenectomy infection rates per 100 person years exposure (PYE)*

	All splenectomy indications				Splenectomy for trauma†			
First author*	PYE	Incidence sepsis/100 PYE	Mortality sepsis/100 PYE	Incidence OPSI‡/100 PYE	PYE	Incidence sepsis/100 PYE	Mortality sepsis/100 PYE	Incidence OPSI‡/100 PYE
O'Neal[14]	944	ns	0·74	ns				
Schwartz[7]	1090	4·77	0·09	0·09	303	3·30	0	0
Standage[15]	879	ns	2·28	ns				
Pedersen[19]	2381	0·88	0·25	ns				
Malangoni[20]	1203	0·25	0	0	1203	0·25	0	0
Chaikof[10]	4837	ns	0·70	0·08				
Sekikawa[11]	1406	0·57	0	0	1406	0·57	0	0
Green[12]	734	1·91	0·14	0·14	734	1·91	0·14	0·14‡
Green[34]	105	1·90	0	0·95	105	1·90	0	0·95
Present study (P)	7825	0·42	0·08	0·04	3855	0·21	0·03	0·03
Combined	21 404	0·89†††	0·35	0·06†††	7246	0·59	0·03	0·04

See footnotes to *Table 4*

42 per cent of cases in this study occurred >5 years after splenectomy. All who have undergone splenectomy should receive polyvalent pneumococcal vaccine. This should be given in elective situations as soon as a decision is made to proceed to splenectomy and in an emergency just before discharge from hospital. The protection from vaccination is not complete and there have been many cases of pneumococcal infections following vaccination, some fatal[11,19,23,26–30]. Meningococcal and *Haemophilus* vaccines may be considered, but they have a narrow serotype coverage.

Long-term prophylactic antibiotics (such as phenoxymethyl penicillin) may not prevent severe late postsplenectomy infection as not all infections are caused by organisms sensitive to penicillin. Forty-two per cent of severe late postsplenectomy infections occurred >5 years after splenectomy; long-term patient compliance is a problem and there are case reports[29,30] of fatal pneumococcal sepsis despite penicillin prophylaxis. Early recognition and treatment of infection, as advocated by Duncombe *et al.*[31], may be more effective. The patient is given a supply of amoxycillin 500 mg tablets with instructions to take two tablets at the onset of the first symptom of *any* illness or fever. Amoxycillin has a better absorption and a wider spectrum of activity than phenoxymethyl penicillin. Education of the medical profession and patients is essential to minimize delay in referral as only by having a high level of suspicion can overwhelming postsplenectomy infection be recognized and aggressive therapy instituted, thereby reducing the severity of infection and hopefully halting progression to overwhelming postsplenectomy infection.

The low incidence of severe late postsplenectomy infection and overwhelming postsplenectomy infection, especially after splenectomy for trauma, makes statistical evaluation of the efficacy of prophylactic antibiotics, vaccination and splenic salvage virtually impossible because of the large number of patients required to detect statistically significant differences in incidence.

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Paget's disease of the nipple

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A total of 48 women with Paget's disease of the nipple (nipple eczema containing Paget cells but without a palpable lump) presented to one surgeon over a 13-year period. Temporary healing of the nipple eczema occurred in six patients. In all, 21 of 34 patients with in situ *(DCIS) or invasive ductal carcinoma had mammographic abnormalities. Treatment was by simple mastectomy (37 cases), cone excision of the nipple-areola complex (ten cases) and tamoxifen (one case). DCIS was found in 45 operative specimens (96 per cent); eight had associated invasion. The DCIS was predominantly large cell solid/comedo in type and was multifocal in seven cases (19 per cent). At a median (range) follow-up of 56 (18–96) months, four of the ten patients treated by cone excision have developed a local recurrence, two of these patients have also developed metastases. Two of the 37 patients who underwent mastectomy developed loco-regional recurrences; both had invasive foci at their first operation and remain disease free at 8 years. We no longer feel that cone excision is appropriate treatment.*

Sir James Paget[1] first recognized the relationship between chronic eczema of the nipple and underlying impalpable breast carcinoma in 1874. The clinical features had been described in 1856 by Velpeau[2]. The characteristic large, clear intraepidermal Paget cell may occur through two mechanisms: (1) derivation from an underlying breast carcinoma with migration upwards to the epidermis along the mammary ducts[3–5], and (2) *in situ* malignant change of intraepidermal cells[6,7]. Although unresolved, the former hypothesis is widely accepted as correct. Immunohistochemical studies favour a mammary origin[8]. Conservative surgery would seem inappropriate if the former hypothesis were correct. In an attempt to determine the optimal surgical approach of this uncommon malignancy we have reviewed the clinical and pathological features of all cases of Paget's disease presenting without palpable lumps to this unit during the past 13 years.

Patients and methods

A total of 48 women with Paget's disease of the nipple were treated at the City Hospital, Nottingham between 1973 and 1989, representing 2.6 per cent of all primary breast cancers treated during the same period. Patients with histological evidence of Paget's disease in association with a palpable carcinoma were excluded.

Clinical data were obtained by reviewing the case notes of all patients. All underwent a nipple biopsy under local anaesthetic Definitive treatment consisted of simple mastectomy with node biopsy in 37 patients During the early part of this series, conservative surgery (excision of the nipple–areola complex and a cone of underlying breast tissue) was offered to those patients whose mammograms suggested *in situ* changes to be confined to the immediate nipple area, if no intraduct carcinoma was present at the deep excision edge no further procedure was undertaken. Ten patients chose this treatment option. One elderly patient received tamoxifen alone.

The histological sections from all 48 patients were reviewed by two pathologists (C.W E and I.O E.) to verify the diagnosis and document *in situ* and invasive elements, the type of *in situ* carcinoma was recorded Lymph nodes removed during operation were evaluated for metastatic involvement

Results

The median (range) age at diagnosis was 62 (35–85) years Presentation was by a history of nipple discharge, crusting, bleeding or erythema ranging from 1 month to 12 years (median 6 months); all lesions were unilateral. Three patients had been treated by topical steroids. No nipple abnormality was found in six patients who gave a history of nipple eczema which had healed; four were discharged without biopsy but returned 9–36 months later with recurrent symptoms and signs. Mammograms suggestive of *in situ* disease prompted the nipple biopsy and diagnosis of Paget's disease in the remaining two patients. Preoperative mammography was performed in 37 patients. Mammograms were reported as suspicious of *in situ* or invasive carcinoma in 21 patients (*Table 1*).

Histology

Intraepidermal Paget cells were found in all 48 nipple biopsies; associated DCIS was seen in 23 biopsies. Histological review of the operative specimen revealed *in situ* disease in 35 of 37 mastectomy specimens and all ten cone excisions; the *in situ* component was entirely of the large cell type being predominantly solid in 36 cases and comedo in six. Seven patients had widespread DCIS throughout the breast. Invasive elements were found in seven mastectomy specimens and in one cone excision. Regional lymph nodes were negative in the 47 patients sampled. Despite exensive sampling, underlying DCIS was not identifyed in two mastectomy specimens.

Follow-up

The group undergoing mastectomy had a median (range) follow-up of 40 (7–124) months and in the conservatively treated group it was 56 (18–96) months.

Thirty-five patients treated by simple mastectomy have remained recurrence free; two developed an invasive recurrence, one a spot recurrence at 24 months and the other an axillary node at 13 months. Both had an invasive component within the mastectomy specimen. These patients were treated by local surgery and radiotherapy and remain disease-free at 90 and 96 months respectively.

Four of ten patients treated by cone excision developed a recurrence, one patient with Paget's disease in the scar after 8

Table 1 *Correlation of histological and mammographic findings*

	Histological findings	
Mammogram	DCIS/invasive ($n=45$)	Paget's only ($n=2$)
Suspicious	21	–
Normal	13	–
Not performed	11	2

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months and three with invasive carcinomas at the site of the primary excision. The recurrent Paget's disease was excised: the patient remains disease free at 39 months. The invasive recurrences at 8, 9 and 19 months were treated by simple mastectomy; two had involved axillary nodes. The first patient developed skeletal metastases at 54 months, the second died from liver metastases at 18 months, the latter has no evidence of disease 52 months later.

The Paget's disease in the patient treated by tamoxifen alone remains unchanged after 21 months.

Discussion

The treatment of Paget's disease without a palpable breast lump remains unclear because of a paucity of knowledge concerning its pathogenesis and malignant potential. Improvement or temporary healing of the nipple eczema, as seen in six of our patients, does not preclude the diagnosis and a nipple biopsy is advised for patients who give a history suggestive of Paget's disease.

Lagios *et al.*[9] reported five patients with neither palpable nor mammographic lesions who were treated by excision of the nipple-areola complex only; all but one remained disease free at an average follow-up of 50 months. Paone *et al.*[10], although advocating Patey mastectomy, described five patients treated by excision of the nipple and wedge resection of the underlying breast for localized disease; all remained disease free. In this series four of ten patients treated by cone excision developed recurrence, three of which were invasive.

The solid/comedo large cell size subtype of DCIS is described as the commonest and the most biological aggressive subtype, frequently containing microinvasive elements[11] and pronounced abnormalities in nuclear pleomorphism and mitotic rate[12–14]. Large cell morphology is also associated with amplification of the proto-oncogene c-erbB-2[15,16], a marker for more aggressive behaviour in invasive tumours[17,18]. This oncoprotein is expressed in 91 per cent of women with Paget's disease[19]. Paget's disease appears to be exclusively associated with this solid/comedo subtype.

The treatment of Paget's disease must take into account aetiological concepts of the disease, histological data and epidemiological information. In this present study, DCIS or infiltrating ductal carcinoma was found in 45 of 47 patients presenting with nipple changes and all were of large cell type (predominantly solid in 36) In seven of 37 mastectomy specimens (19 per cent) the DCIS was extensive. Eight specimens contained invasive carcinoma of the breast.

Mammography was unhelpful: 11 of 34 patients with histological evidence of an underlying carcinoma had a normal mammogram. Normal appearances were also seen in one patient with extensive DCIS, and in three of the four patients treated by cone excision who later developed a recurrence. Two patients who had clinically normal nipples at their first clinic attendance had suspicious mammographic microcalcifications. Detailed histological examination including the nipple failed to demonstrate an underlying *in situ* or invasive carcinoma in two patients treated by mastectomy. Other studies have identified *in situ* and invasive elements in 100 per cent of mastectomy specimens[7,8,10,20] but these employed serial sectioning techniques through the entire nipple and operative specimen.

The 40 per cent recurrence rate following conservative surgery, the high rate of invasive components found (17 per cent) and the extensive DCIS (19 per cent) of mastectomy specimens in this series supports the view of others[7,8,10,20] who advocate simple mastectomy. Subcutaneous mastectomy with nipple excision may be an alternative where a better cosmetic appearance is sought

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Deep vein thrombosis: effect of graduated compression stockings on distension of the deep veins of the calf

The mechanisms by which graduated compression stockings prevent deep vein thrombosis are not completely understood. Recent work has suggested that venous distension plays a role in initiating the process. Our previous work has shown that the deep veins of the lower limb distend in patients undergoing surgical procedures. We have investigated 40 patients receiving surgical treatment on the abdomen or neck. A medial gastrocnemius vein was studied using ultrasound imaging during the operations. In half the patients a graduated compression anti-embolism stocking was applied to the limb under study at the start of the operation, immediately after initial measurements of vein diameter. The median vein diameter in both groups was the same at the start of the operative procedures (control, 2·6 mm, interquartile range 2·1–3·3 mm; stocking, 2·6 mm, interquartile range 2·1–3·7 mm). After application of a stocking the median diameter in this group fell to 1·6 mm (interquartile range 1·3–2·8 mm) and then decreased slightly at the end of the operation. In the control group the vein diameter increased to 2·9 mm (interquartile range 2·3–4·0 mm) during the operative procedure.

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Deep vein thrombosis remains a common cause of death in hospital patients in the UK although the diagnosis may only be suspected in a very small proportion of these patients[1]. Deep vein thrombosis is a hazard for surgical patients in many specialities as well as those being treated in medical wards for common conditions such as myocardial infarction and strokes[2–4]. The means of reducing the hazard to hospital patients are well known and their efficacy has been tested[5,6]. Subcutaneous injections of heparin are effective but may cause patient discomfort and occasionally severe haemorrhage[7]. Anti-embolism stockings also reduce the risk of deep vein thrombosis and do not carry an associated risk of haemorrhage or cause discomfort to the patient[8].

The efficacy of heparin probably lies in its ability to promote antithrombin III activity, which along with the other inhibitors of thrombosis tends to decline in activity during surgical procedures and times of stress[9]. The means by which stockings achieve their effect remains to be fully explained It has been shown that they increase the flow velocity in the femoral vein[10] but this may not be their only mechanism of action. Certainly, the compression gradient is essential since inadequatly designed stockings may be ineffective[11]. Recently it has been shown that there is an association between venous distension in the upper limb and subsequent deep vein thrombosis of the lower limb[12]. It has been suggested that the mechanism which results in the development of deep vein thrombosis is the production of subliminal endothelial damage, produced by stretching of the vein. Our own observations have confirmed that venous distension occurs in lower limb veins during the course of surgical procedures[13].

This investigation was designed to determine whether graduated compression stockings prevent the venous distension we had seen previously.

Patients and methods

A total of 41 patients undergoing a variety of surgical procedures were investigated (*Table 1*). After induction of anaesthesia, images of the medial gastrocnemius veins were obtained using the 7 MHz linear array transducer of an Acuston 128 ultrasound scanner (Acuson, Mountain View, California, USA) with the patient supine on the operating table. When a suitable vein was identified, the transducer was held in place using a clamp firmly attached to the operating table. Care was taken to ensure that the transducer exerted no compression on the limb under investigation, a factor which might result in alteration of the vein diameter. This was achieved by clamping the transducer 1–3 mm from the skin and filling the gap with acoustic scanning jelly. Patients were randomly allocated to receive a TED stocking (Kendall Healthcare Products Company, Mansfield, Massachusetts, USA) or no additional prophylaxis. The stocking was applied to the limb under study by slight abduction away from the transducer during the application process. The limb was then replaced in contact wth the transducer to regain a view of the gastrocnemius vein, after application of a suitable quantity of acoustic scanning jelly. Subsequently, the vein under study was maintained in constant view and the diameter noted at 5–min intervals until the operative procedure was completed. All patients received appropriate alternative prophylactic measures to prevent deep vein thrombosis where indicated, usually in the form of low-dose subcutaneous heparin

The flow velocities in the gastrocnemius veins could not be measured accurately even using the low flow velocity measuring capability of the ultrasound machine which indicates velocities of 5 mm or greater and is satisfactory in the assessment of axial veins such as the popliteal or posterior tibial vessels Clearly the flow rates in these veins were very low during anaesthesia so flow velocity data have not been considered further in this study

Table 1 *Patients studied and operations performed*

	Controls	TED stocking
Number of patients	20	21
Men	5	9
Women	15	12
Mean age (range) (years)	46 (17–73)	55 (26–74)
Operations		
Laparotomy	5	6
Head and neck procedures	5	4
Herniorrhaphy	4	6
Vascular access	6	5

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Patients gave their informed consent to inclusion in the study Data were analysed using the Wilcoxon matched-pairs signed-rank test for within-subject comparison

Results

Details of the patients and of the operative procedures carried out are shown in *Table 1*. The changes in diameter during the course of the operation are shown in *Figure 1* in which the stocking and control groups are compared. Initially, the diameter of gastrocnemius veins was the same in the control and stocking groups after induction of anaesthesia but before the start of the operative procedure (control: median, 2·6 mm; interquartile range (IQR) 2·1–3·3 mm; stocking: median, 2·6 mm; IQR, 2·1–3·7 mm). In the stocking group there was an immediate reduction in vein diameter in response to application of the garment which applies 18 mmHg compression at the ankle and 8 mmHg at the upper calf. The median vein diameter fell to 1·6 mm (IQR, 1·3–2·8 mm), a median reduction of 32 per cent (IQR, 19–49 per cent) which is highly statistically significant ($P=0{\cdot}0001$, Wilcoxon). During the course of the operative procedure there was a further decrease in vein diameter to 1·5 mm (IQR, 1·0–2·2 mm) which represents a decrease of 5·5 per cent (IQR, 0–15 per cent) compared with that immediately after the application of the stockings, $P=0{\cdot}026$ (Wilcoxon). The total reduction in vein diameter seen in this group was 48 per cent (IQR, 26–53 per cent) between induction of anaesthesia and the end of the operation.

The patients in the control group showed the same capability to undergo distension of the gastrocnemius veins during surgical procedures that we have previously observed[13]. The median distension seen during this study between induction of anaesthesia and the end of the operation was 19 per cent (IQR, 6·9–29 per cent) to 2·9 mm (interquartile range 2·3–4·0 mm), $P=0{\cdot}0005$ (Wilcoxon).

Discussion

Previous investigations into the mode of action of graduated compression stockings in preventing deep vein thrombosis have shown that, using an appropriate compression profile, a substantial increase in femoral vein velocity measured by Doppler ultrasound can be obtained[14]. These data suggest that venous emptying of the calf can be optimized by this method of prophylaxis. This has been confirmed in studies using radioisotope clearance which have shown that graduated compression stockings achieve much greater efficiency of emptying than limbs without support in recumbent subjects[15]. The flow velocity in veins of the lower limb during recumbency has been estimated to be in the range of 2–5 cm/s from isotope injections into dorsal foot veins when blood is directed into the deep veins by an ankle tourniquet[15]. By comparison, radiological studies have shown persistance of contrast medium for 10–30 min in the deep veins of the leg following injection[15,16]. The effect of graduated compression stockings is substantially to decrease the time taken to clear the contrast The reasons for the discrepancy in isotope transit time and contrast clearance are not clear. This may be due to the high density of the radiographic contrast media used which are consequently rather difficult for the slow venous circulation to remove. Alternatively, the isotope technique reflects flow in the main axial veins of the limb, whereas the retained contrast may lie principally in the gastrocnemius and soleal veins.

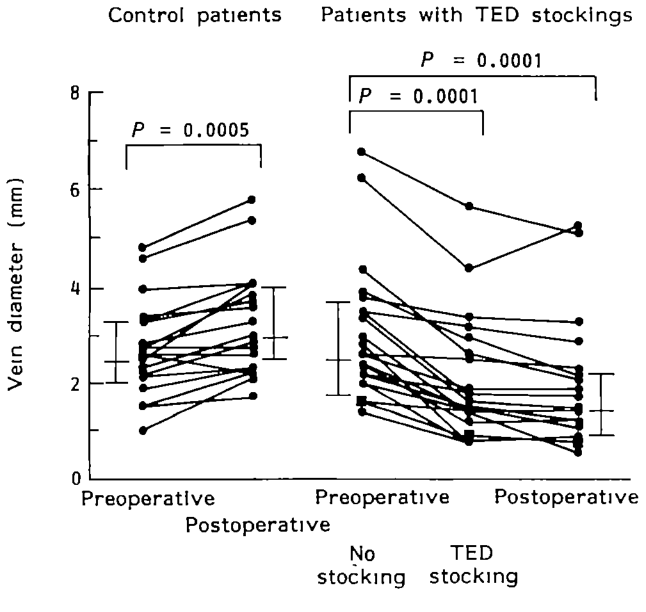

Figure 1 *Vein diameters at the start and end of surgical procedures in the control and TED stocking groups There is distension in the control group, but a marked decrease in diameter in the stocking group*

The efficacy of ultrasound imaging in studying the lower limbs has been the subject of extensive study in our department. We have been able to show previously that venous distension occurred during operations, but we experienced some difficulty in ensuring that precisely the same segment of vein was studied on each occasion. This was overcome in the present study by investigating only one vein at a time without removing the transducer between observations. This limits the movement between transducer and patient to a small amount, essential when studying veins in the range 2–5 mm in diameter. The wavelength of ultrasound at 7 MHz in human tissues (about 0·25 mm) permits an accurate estimate of the vein diameter to be made The ultrasound machine employed in this study indicates dimensions to a resolution of 0·1 mm, therefore small changes in vein diameter could easily be detected. It was disappointing that flow velocities could not be measured reliably in the gastrocnemius veins, but we felt justified in studying these vessels since this is the location where DVTs are thought to originate and our previous investigations showed that these were the most likely to distend. It seems probable that the slow clearance of radiographic contrast material from this region observed by previous authors is due to the low flow velocities in these vessels. So far other groups of veins have not been investigated by continuous imaging Although it is desirable to understand the effects of anti-embolism stocking on the axial veins, we were restricted in this study to examining one vein per patient which has limited the total number of anatomical sites investigated.

The recent demonstration of the association of postoperative deep vein thrombosis and venous distension in the upper limb suggested a possible mechanism for producing endothelial damage which might precipitate deep vein thrombosis[12], assuming that such processes also affected the veins of the lower limb. We were previously able to confirm that lower limb vein distension did occur during surgical procedures. The gastrocnemius veins seemed to be most greatly affected by this phenomenon and the degree of distension was increased by the administration of intravenous saline, a factor which has previously been associated with a predisposition to deep vein thrombosis[17].

Virchow[18] originally associated deep vein thrombosis with venous stasis, changes in the blood and damage to the vein wall. The haematological abnormalities leading to postoperative deep vein thrombosis include decreased levels of the coagulation inhibitors protein C, protein S and antithrombin III[9]. Stasis is most prominent in the valve sinuses[16] and thrombosis frequently occurs first in the soleal and gastrocnemius veins where flow is probably only rapid under conditions of exercise. Certainly in this study the flow velocity in all patients was not greater than 5 mm/s, corresponding with the minimum velocity which our machine could register. It seems likely that this might render these vessels particularly sensitive to deep vein thrombosis.

There can be no doubt that TED stockings resulted in an impressive reduction in diameter of the gastrocnemius veins in the patients studied, amounting in total to a median of 48 per cent (IQR, 26–53 per cent) of the original size. This clearly will have a substantial effect on the emptying and flow in these vessels. In addition, no venous distension occurred during the operation in the stocking group; in fact the gastrocnemius veins showed a small decrease in diameter. The stockings would provide protection from the effects of venodilation seen in the control group, and suggested by Comerota *et al*[12] as a cause of endothelial injury and hence deep vein thrombosis.

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Combined portal vein and liver resection for carcinoma of the biliary tract

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Twenty-nine patients with advanced carcinoma of the bile duct or gallbladder underwent combined portal vein and liver resection. Segmental excision of the portal vein was performed in 16 cases and wedge resection of the vessel wall in 13. The operative mortality rate was 17 per cent. The median survival for the 24 patients who left hospital was 19·8 months. Actuarial survival rates at 1, 3 and 5 years for all 29 patients were 48 per cent, 29 per cent, and 6 per cent respectively, whereas the median survival for 46 patients with unresectable carcinoma was 3 months and the 1 and 3-year actuarial survival rates were 13 per cent and zero respectively. This difference in survival times between patients undergoing hepatectomy with portal vein resection and those with unresectable carcinoma were statistically significant (P<0·01). Combined portal vein and liver resection is recommended as a reasonable surgical approach in selected patients with advanced carcinoma of the biliary tract.

Although carcinoma of the hepatic hilus is generally a slow-growing tumour[1], it has a poor prognosis. Furthermore, advanced carcinoma of the gallbladder has been regarded as a disease usually resulting in rapid death. Despite recent advances in techniques for diagnosing hepatobiliary diseases, carcinoma of the biliary tract is still frequently first encountered at an advanced stage. Aggressive surgical approaches to carcinoma of the hepatic hilus using liver resection have been used by many surgeons with varying degrees of success[2–16], and radical surgery has not conferred any advantage on patients with invasive carcinoma of the gallbladder[17–19] In an effort to prolong and improve the quality of survival, we have attempted combined liver resection with vascular resection and reconstruction to remove advanced carcinomas of the biliary tract.

Patients and methods

From October 1975 to December 1989, 216 patients with biliary tract carcinoma were treated at the First Department of Surgery, Nagoya University Hospital. Among these 216 patients, surgical resection was possible in 170 cases (78·7 per cent) 95 of 118 patients (80·5 per cent) with bile duct carcinoma were resected, and 75 (76·5 per cent) of 98 patients with gallbladder carcinoma Hepatectomy was performed in 107 (62·9 per cent) of the 170 patients. Twenty-nine of the 107 patients underwent combined portal vein and liver resection for advanced carcinoma of the biliary tract Sixteen of the 29 had bile duct carcinoma, and the remaining 13 had gallbladder carcinoma. Among these 29 patients, 11 were men and 18 were women Their ages ranged fom 33 to 76 years, with a mean age of 59·8 years

The general condition of each patient was carefully assessed and special attention paid to laboratory values of their liver function tests. During the period of preoperative investigations, jaundice was reduced to levels below 3·0 mg/l of the total bilirubin level by percutaneous transhepatic biliary drainage. Selective arteriography, percutaneous transhepatic portography, and selective hepatic venography were performed to investigate anatomical variation and tumour involvement of vessels.

The 29 portal vein resections are depicted diagrammatically in *Figure 1* The method of resection was governed by the extent of tumour involvement of the portal vein. extensive involvement necessitated segmental excision (16 cases) while wedge resection was performed when there was minimal vein involvement (13 cases)

For segmental excision of the portal vein and end-to-end anastomosis, the superior mesenteric artery was temporarily clamped. An end-to-end anastomosis was performed by a continuous extraluminal over-and-over suture of 5/0 polypropylene using two guy stitches (*Figure 2*) When the distal vascular clamp was placed on the base of the umbilical portion of the portal vein, the vascular clamp was placed obliquely to the portal vein. The main trunk of the portal vein was cut transversely, but the hepatic side of the portal vein was either cut obliquely or bevelled so as to provide a large lumen to adjust the calibre of the two ends (*Figure 3*)

The range of hepatic resection for carcinoma of the hepatic hilus was determined by the extent of cancer in the segmental bile ducts Hepatopancreatoduodenectomy[20] was performed in six of the 16 cases of bile duct carcinoma (*Table 1*)

Combined portal vein and liver resection for advanced carcinoma of the gallbladder was performed in 13 cases Segmental excision of the portal vein and end-to-end anastomosis were carried out in 11 of these cases. The range of hepatic resection depended on the degree of cancer involvement of the liver. Hepatopancreatoduodenectomy was performed in seven of these 13 cases (*Table 2*).

In the assessment of survival, life table analysis has been used and the statistical significance of results assessed by the generalized Wilcoxon test.

Results

The mean(s.d.) duration of hospital stay for the 29 patients who underwent combined portal vein and liver resection for biliary tract carcinoma was 71·7(34·6) days, range 16–218 days. Of the 79 patients who did not undergo portal vein resection the stay was 63·6(27·6) days, range 11–155 days, and for the 46 patients who had an unresectable cancer the stay was 72·5(68·2) days, range 5–447 days. These differences were not statistically significant.

All 26 postoperative complications occurred in 19 (66 per cent) of the 29 patients (*Table 3*) The most common complications were hepatic failure requiring plasma exchange (eight patients), wound infection (six patients), and anastomotic insufficiency (five patients) at the pancreatojejunostomy and/or intrahepaticojejunostomy Five of the eight patients who developed postoperative hepatic failure died within 30 days of operation (operative mortality rate of 17 per cent). The cause of the acute hepatic failure was suspected hepatic ischaemia occurring during the operation. The median survival for the 24 patients who were discharged from hospital after combined portal vein and liver resection for carcinoma of the biliary tract was 19·8 months. The 1, 3, and 5-year survival rates for all 29 patients were 48 per cent, 29 per cent, and 6 per cent respectively. The median survival for 73 patients who survived

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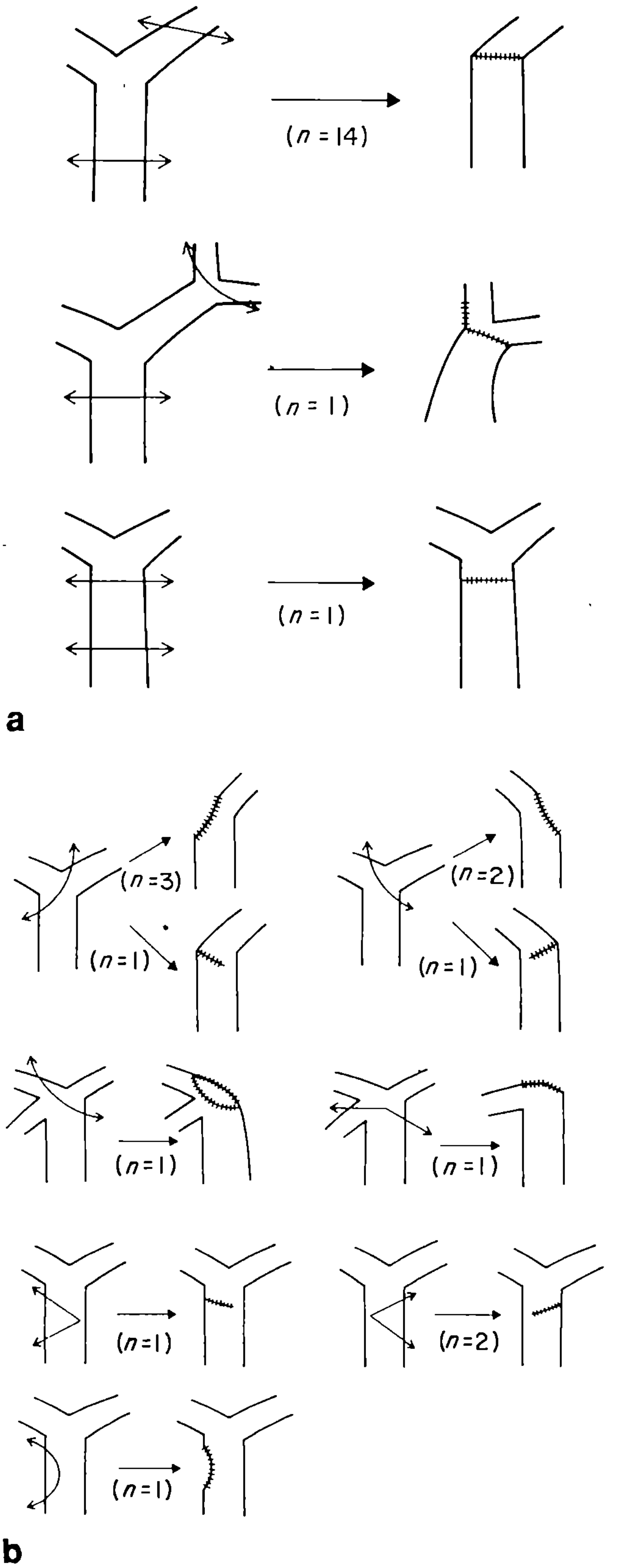

Figure 1 *Combined resection and reconstruction of portal vein* **a** *End-to-end anastomosis was performed in 16 cases of segmental excision,* **b** *the side wall was sutured parallel to the axis in five of 13 cases of wedge resection. A saphenous vein patch was used in one case*

hepatectomy without portal vein resection was 31 months. The 1, 3, and 5-year survival rates for all 78 patients were 67 per cent, 40 per cent, and 30 per cent respectively, while the median survival for 46 patients with unresectable carcioma of the biliary tract was 3 months, and 1 and 3-year survival rates for all these 46 patients were 13 per cent and zero respectively (*Figure 4*). These differences in survival times between patients undergoing hepatectomy with or without portal vein resection and those with unresectable carcinoma of the biliary tract were statistically significant ($P<0{\cdot}01$, $P<0{\cdot}001$).

The median survival for the 14 patients with bile duct carcinoma who survived combined portal vein and liver

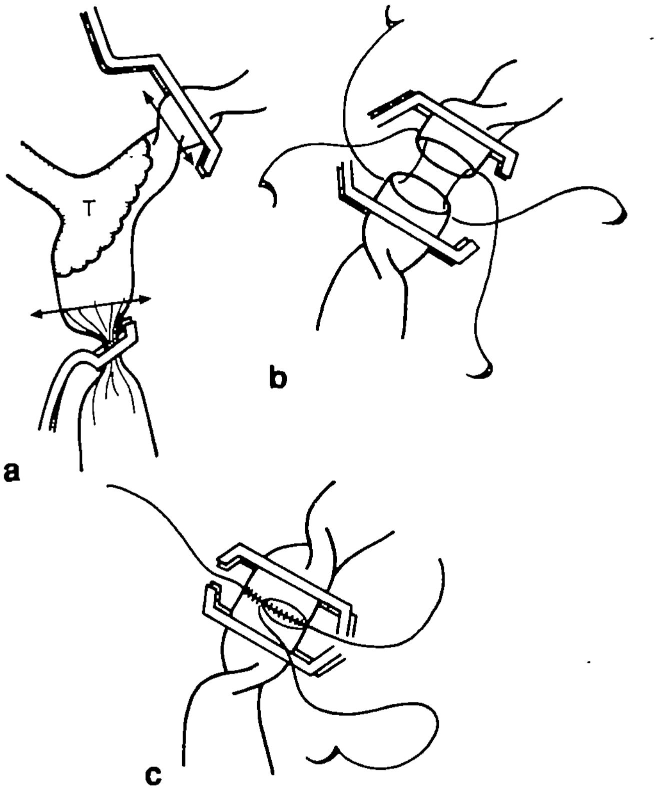

Figure 2 *Resection and reconstruction of the portal vein* **a** *Vascular clamps were applied perpendicularly to the portal vein,* **b, c** *end-to-end anastomosis was performed after turning the clamps to the right and left to assure frontal exposure of the right and left walls. T, tumour*

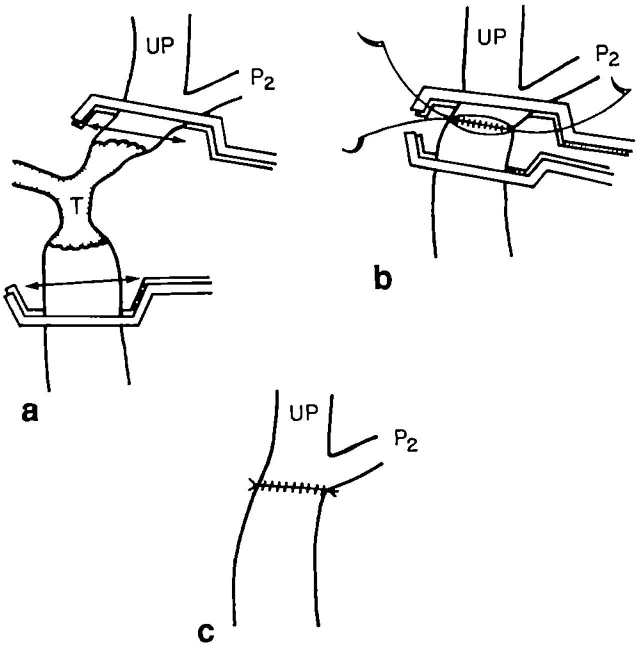

Figure 3 *Resection and reconstruction of the portal vein.* **a** *The distal clamp was placed on the base of the umbilical portion* **b, c** *Posterior anastomosis was carried out using the intraluminal technique* P_2, *lateral posterior branch, T, tumour, UP, umbilical portion*

Table 1 *Combined portal vein and liver resection for advanced carcinoma of the hepatic hilus*

Resected part of portal vein	Operative procedure	No of cases
Segmental excision		
Main trunk of portal vein–left portal vein	Right hepatic trisegmentectomy, caudate lobe resection	2
	Extended right hepatic lobectomy, caudate lobe resection, pancreatoduodenectomy	2
	Right hepatic lobectomy, caudate lobe resection	1
Wedge resection		
Main trunk of portal vein	Left hepatic trisegmentectomy, caudate lobe resection	1
	Right hepatic lobectomy, caudate lobe resection, pancreatoduodenectomy	1
	Extended right hepatic lobectomy, caudate lobe resection pancreatoduodenectomy	1
Main trunk of portal vein–left portal vein	Right hepatic trisegmentectomy, caudate lobe resection, pancreatoduodenectomy	1
	Extended right hepatic lobectomy, caudate lobe resection, pancreatoduodenectomy	1
	Right hepatic lobectomy, caudate lobe resection	1
Main trunk of portal vein–right portal vein	Left hepatic trisegmentectomy, caudate lobe resection	1
	Extended left hepatic lobectomy, caudate lobe resection	2
	Left hepatic lobectomy, caudate lobe resection	1
Main trunk of portal vein–right anterior portal vein*	Extended left hepatic lobectomy, caudate lobe resection	1

* Saphenous vein patch

Table 2 *Combined portal vein and liver resection for advanced carcinoma of gallbladder*

Resected part of portal vein	Operative procedure	No of cases
Segmental excision		
Main trunk of portal vein–left portal vein	Right hepatic trisegmentectomy, caudate lobe resection, pancreatoduodenectomy	1
	Right hepatic trisegmentectomy, caudate lobe resection. bile duct resection	1
	Extended right hepatic lobectomy, caudate lobe resection, pancreatoduodenectomy	5
	Extended right hepatic lobectomy, caudate lobe resection bile duct resection	3
Main trunk of portal vein	Left medial inferior and right anterior inferior segmentectomy, bile duct resection	1
Wedge resection		
Main trunk of portal vein–left portal vein	Extended right hepatic lobectomy, pancreatoduodenectomy	1
Main trunk of portal vein	Right anterior segmentectomy, caudate lobe resection	1

Table 3 *Postoperative complications*

Complication	No. of patients
Hepatic failure	8
Wound infection	6
Anastomosis insufficiency	5
Bile leakage from liver stump	2
Cholangitis	2
Right subphrenic abscess	1
Respiratory insufficiency	1
Renal failure	1

resection was 23·5 months. Ten patients died of recurrent tumour at 5–95 months, while three patients died after 3–24 months from various causes unrelated to carcinoma, including prolonged hepatic failure, hepatic abscess, and bleeding oesophageal varices. Only one patient is alive with a recurrent tumour 43 months after right hepatic lobectomy with total caudate lobectomy and segmental excision of the portal vein. The 1, 3, and 5-year survival rates for all 16 patients were 56 per cent, 42 per cent, and 9 per cent respectively. Sixty-one patients undergoing hepatectomy with or without portal vein resection for carcinoma of the bile duct survived significantly longer than 23 patients with unresectable bile duct carcinoma ($P<0.05$, $P<0.001$) (*Figure 5*)

The median survival for the ten patients with gallbladder carcinoma who survived combined portal vein and liver resection was 18·6 months. Four patients died of a recurrent tumour at 6–20 months, and three patients died at 2–24 months from prolonged hepatic failure and ileus without evidence of recurrent tumour. Three patients are alive and well 9, 24, and 43 months after surgery. The 1, 3 and 5-year survival rates for all 13 patients were 38·5 per cent, 15·4 per cent and zero.

The median survival for 30 patients with gallbladder carcinoma who survived hepatectomy without portal vein resection was 12·1 months, while that for 23 patients with unresectable gallbladder carcioma was 3 months. There were no statistically significant differences between patients with portal vein and liver resection and those with unresectable carcioma However, 33 patients undergoing hepatectomy without portal vein resection survived significantly longer than the 23 patients with unresectable carcinoma ($P<0.001$) (*Figure 6*).

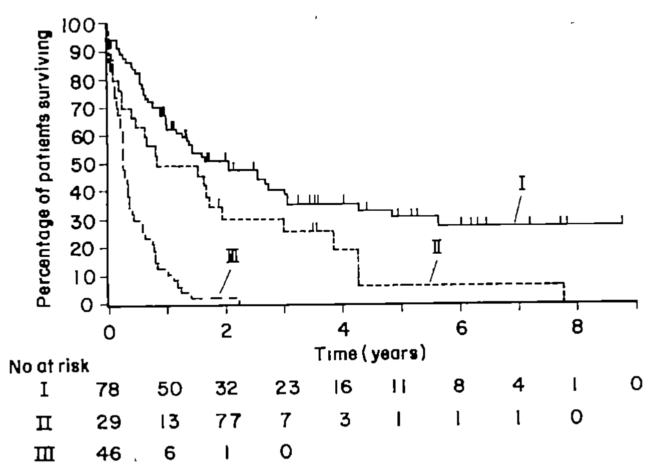

Figure 4 *Postoperative life table survival curves according to type of treatment in patients with carcinoma of the biliary tract I, hepatectomy without portal vein resection, II, hepatectomy with portal vein resection, III, unresected cases Differences between groups I and III* ($P<0.001$) *and between groups II and III* ($P<0.01$) *are statistically significant*

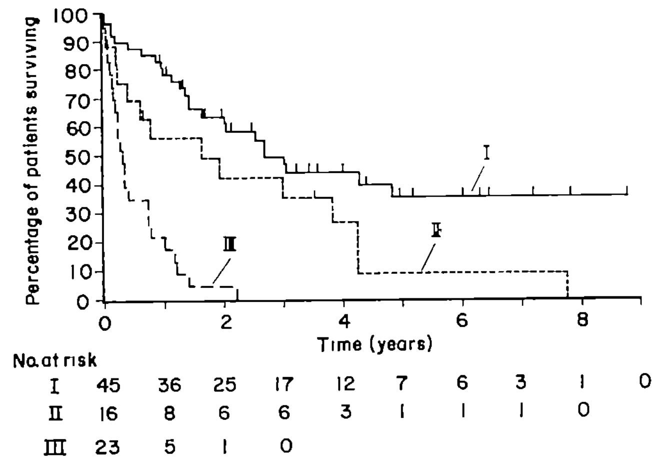

Figure 5 *Postoperative life table survival curves according to type of treatment in patients with bile duct carcinoma I, hepatectomy without portal vein resection, II, hepatectomy with portal vein resection, III, unresected cases Differences between group I or II and III are statistically significant* (*I* versus *III*, $P<0.001$, *II* versus *III*, $P<0.05$)

Discussion

The report of Longmire *et al* [2] in 1973 encouraged hepatobiliary surgeons to attempt combined liver and vascular resection for advanced carcinoma of the bile duct. Others have reported the use of hepatectomy with combined resection of the portal vein and/or hepatic artery using vascular surgical techniques to allow curative surgery in the treatment of advanced carcinoma of the biliary tract[3,6,9,10,21,22].

While there are various techniques for reconstruction following portal vein resection, the easiest procedure after wedge resection involves the use of lateral clamping of the vessel and longitudinal suturing of the venotomy. Care must be taken, however, to avoid postoperative stenosis. Therefore, a longitudinal venotomy should be closed parallel to the portal vein axis to maintain sufficient diameter after wedge resection.

Vascular reconstructive techniques after segmental excision include end-to-end anastomosis and interposition of the splenic or iliac vein Sakaguchi and Nakamura[21] have proposed an 'insert anastomosis' using interrupted sutures in an end-to-end anastomosis between the main trunk and the left portal vein as a means of preventing postoperative stenosis However, we prefer to adopt the technique whereby fine anastomosis is accomplished by providing a 'growth factor'[23] of 2–3 mm on each of the anterior and posterior walls by continuous sutures with two guy stitches. Lygidakis *et al.*[22] have also reported aggressive surgical procedures including various types of combined resection and reconstruction of the portal vein and hepatic artery for advanced carcinoma of the hepatic hilus They used direct end-to-end anastomosis or venous transplants interposed between the transected margins of the portal vein and/or hepatic artery.

Percutaneous transhepatic biliary drainage, endoscopic retrograde biliary drainage, and surgical bilioenteric anastomosis are still frequently attempted for advanced carcinoma of the hepatic hilus which involves the portal vein. However, the prognosis in such cases is extremely poor, with death usually from cholangitis and/or hepatic failure. Fortner *et al.*[4], Pichlmayr *et al.*[24], and Ringe *et al.*[25], on the other hand, have attempted liver transplantation for advanced carcinoma of the proximal bile duct without achieving long-term survival cases. Although Tompkins *et al.*[26] and Lai *et al.*[27] have reported that large liver resections accompanying resection of bile duct cancers did not result in significant extension of survival, we have recently reported that our aggressive surgery for these lesions offered unexpectedly long survival periods[28]. As shown in *Figures 4* and *5* statistically significant differences were observed in survival times between patients undergoing hepatectomy with or without portal vein resection and those with unresectable carcinoma of the hepatic hilus. Recently, Pinson and Rossi[14], Hadjis *et al.*[29], and Fortner *et al* [30] have reported favourable long-term survival rates for patients with carcinoma of the hepatic hilus, but other authors have only occasionally had patients survive for >5 years after surgery

Pemberton *et al.*[17], Evander and Ihse[18], and Friedman *et al* [19] have reported that radical surgical extirpation did not benefit patients with carcinoma of the gallbladder. Most patients with unresectable advanced carcinoma of the gallbladder involving the adjacent organs died within 3 months. However, aggressive surgery employing hepatectomy with or without portal vein resection extended the median survival. As shown in *Figure 6* a statistically significant difference in survival times was noted between patients undergoing hepatectomy without portal vein resection and those with unresectable carcinoma of the gallbladder.

As the most common complication among our patients was hepatic failure, improving the critical perioperative period is a problem that remains to be solved. Despite this, we believe that operative indications for carcinoma of the biliary tract should be carefully re-examined, taking into consideration the fact that aggressive surgery could offer unexpectedly long survival.

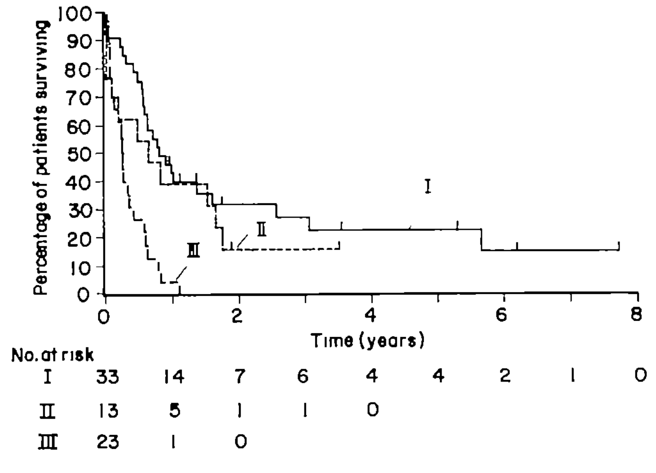

Figure 6 *Postoperative life table survival curves according to type of treatment in patients with gallbladder carcinoma I, hepatectomy without portal vein resection, II, hepatectomy with portal vein resection, III, unresected cases Statistically significant differences are found between groups I and III* ($P<0.001$). *I* versus *II* and *II* versus *III*, *not significant*

In conclusion, combined portal vein and liver resection is to be recommended as a reasonable surgical approach for selected cases of advanced carcinoma of the biliary tract.

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Intra-arterial streptokinase infusion in acute lower limb ischaemia

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Between 1986 and 1988, 38 patients (29 men and nine women), median age 65 years (range 38–85 years), underwent local intra-arterial streptokinase therapy for acute lower limb ischaemia. Three patient groups were identified: 15 with acute on chronic ischaemia (group 1), 12 postangioplasty (group 2) and 11 postfemorodistal bypass (group 3). Distal arteriographic run-off was a significant discriminant between success and failure in group 1 ($n=15$, $\chi^2=11{\cdot}5$, $P=0{\cdot}001$) *and in the overall group* ($n=38$, $\chi^2=17{\cdot}2$, $P<0{\cdot}001$). *In group 2, four patients with good run-off had an unsuccessful outcome; this was due in all cases to technical problems (haemorrhage in two and intimal dissection in two). In group 3, two patients with good run-off had unsuccessful streptokinase infusions. In both cases the graft failed in the early postoperative period (<30 days). By contrast, the four patients whose grafts occluded after 30 days had successful streptokinase infusions and long-term graft patency was achieved by further surgery and balloon dilatation. In all groups, no patient with a poor run-off had a successful outcome following streptokinase administration. The role of local intra-arterial streptokinase therapy in the critically ischaemic limb remains controversial, but these results suggest that an adequate run-off is an important factor in the selection of patients for treatment.*

Transcatheter administration of low doses of streptokinase was first reported by Cotton *et al.* in 1962[1], and subsequently by Chesterman *et al.* in 1971[2]; it was popularized by Dotter *et al.* in 1974[3]. Since then numerous articles have been published describing both the advantages and hazards of streptokinase administration[4–15].

Streptokinase was discovered in 1933 by Tillett and Garner[16], but it was not until 1959 that its potential for clinical application was suggested[17]. The early preparations were plagued by pyrogenic and allergic reactions, but modern purified forms of the drug are associated with an acceptably low rate of allergic reaction[18]. Therapeutically administered streptokinase stimulates an antibody response that makes repeated treatment with the same drug difficult for 4–6 months. In contrast, urokinase is non-antigenic and multiple consecutive courses of treatment are feasible. Despite this, its high cost (5–10 times that of streptokinase) may preclude its frequent use More recently, reports on tissue plasminogen activator suggest that it is a superior thrombolytic agent with fewer side effects[19].

Thrombolytic therapy may be administered intravenously or intra-arterially. Intravenous therapy with high dosage produces a systemic lytic state and has been used for venous thrombosis, pulmonary embolism, myocardial infarction and arterial thrombosis. The major drawback of systemic therapy has been bleeding which occurs in about 10 per cent of patients[18]. The technique of low-dose intra-arterial infusion via an arteriographic catheter impacted into the arterial thrombus has resulted in better clot lysis and fewer haemorrhagic complications[3]. Despite these developments, serious and occasionally fatal bleeding complications still occur[9,20] and risk from haemorrhage is a contraindication to thrombolytic therapy[18].

Apart from the side effects of treatment, one of the main drawbacks of instituting an infusion is that there are no accurate predictors of duration of infusion or successful outcome. Little work has been done to identify those variables and factors which may signify potential success or failure. This paper describes the use of arteriographically assessed run-off as a predictor of outcome of treatment in an attempt to identify those patients who may benefit from local streptokinase therapy.

Patients and methods

A retrospective study was undertaken of 38 patients who had undergone streptokinase therapy for acute arterial occlusion at the Bristol Royal Infirmary between 1986 and 1988 Three patient categories were identified: group 1 consisted of 15 patients presenting acutely with rest pain and with a history of ischaemic symptoms, usually intermittent claudication; group 2 included 12 patients who reoccluded following initially successful percutaneous angioplasty for occlusive disease, and group 3 consisted of 11 patients with occluded femorodistal bypass grafts, all for critical ischaemia.

A transfemoral arteriogram was invariably done to confirm the diagnosis and to position the catheter tip so that it was wedged into the thrombus Streptokinase was infused at a rate of 12000 units/h together with heparin 250 units/h (to reduce catheter-related thrombosis). With the catheter *in situ* and the infusion in progress, the patient was kept on strict bed rest and progress monitored by ward staff who checked the catheter site for signs of bleeding every 30 min Clotting status was checked periodically and the rate of thrombus lysis monitored using repeat arteriograms every 6–12 h, according to the rate of clot lysis. On withdrawal of the infusion, patients were monitored for a further 24-h period If after restoration of patency an arterial or graft stenosis was identified, balloon angioplasty was performed to prevent reocclusion Therapy was stopped when the arteriogram showed complete lysis, or if limb viability deteriorated or if a haemorrhagic complication occurred

A successful outcome was one in which there was angiographic evidence of clot lysis and a clinical improvement in symptoms and signs. An unsuccessful outcome was one in which no lysis occurred, the limb deteriorated clinically, or complications of treatment developed requiring premature cessation of therapy. The outcome of local streptokinase infusion was correlated with run-off distal to the occlusion, assessed on both pre- and poststreptokinase arteriograms. Run-off was quantified by giving one point for each patent vessel in the calf (range 0–3 for each leg) Patients with a run-off score of 1 or less were considered to have a 'poor' run-off, those with a score of 2 or 3 were considerd to have a 'good' run-off

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Table 1 *Outcome of streptokinase infusion related to run-off score in the three groups*

Arteriographic run-off	Outcome	Group 1	Group 2	Group 3	Overall
Good	Success	7	5	4	16
	Failure	0	4	2	6
Poor	Success	0	0	0	0
	Failure	8	3	5	16

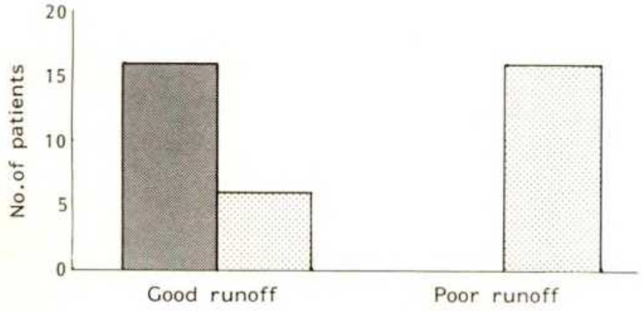

Figure 1 *Outcome of treatment related to run-off in the overall group:* ■, *success;* ▨, *failure*

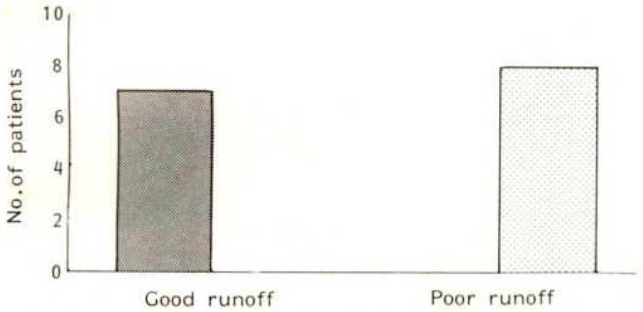

Figure 2 *Outcome of treatment related to run-off in group 1:* ■, *success;* ▨, *failure*

Results

Overall analysis

In the 38 patients studied, the early (<30 days) and late (>30 days) mortality rates were 8 per cent and 11 per cent respectively. Two deaths were directly attributable to streptokinase therapy; one patient suffered a cerebrovascular accident, presumed to be haemorrhagic, and the second had a cardiac arrest following a significant retroperitoneal haemorrhage. Successful local streptokinase infusion was analysed with respect to the distal arterial run-off. In the overall group of 38 patients, there was a significant difference between the arteriographic run-off and a successful outcome following the streptokinase infusion ($\chi^2 = 17{\cdot}2$, $P < 0{\cdot}001$) as shown in *Table 1* and *Figure 1*.

Group analysis

Group 1 (acute on chronic ischaemia). The duration of symptoms ranged from 8 h to 3 months. There was a significant difference between the outcome of streptokinase therapy and the distal run-off score ($n = 15$, $\chi^2 = 11{\cdot}5$, $P < 0{\cdot}001$). All patients with good run-off had successful treatment, whereas in none of the eight patients with poor run-off was there a successful outcome (*Figure 2*).

Group 2 (postangioplasty ischaemia). The duration of symptoms ranged from 4 h to 4 days. There was no correlation between outcome and arteriographic run-off score. Four of the nine patients with good run-off had failed streptokinase infusions. In all cases treatment was withdrawn because of technical problems rather than incomplete lysis, two because of significant haemorrhage and two after intimal dissection. No patient with poor run-off had a successful outcome (*Figure 3*).

Group 3 (postfemorodistal bypass). The duration of symptoms ranged from 7 h to 14 days. Of six patients with good run-off, two failed to respond to streptokinase. In both, graft occlusion had occurred within 30 days of operation suggesting a technical problem with the graft. The remaining four patients with occluded grafts (>30 days) had a successful outcome following streptokinase infusion. All four had good run-off and long-term patency was achieved by a combination of surgery and balloon dilatation. None of the five patients with an occluded graft in the presence of poor run-off had a successful outcome (*Figure 4*).

Discussion

The management of acute arterial occlusion remains a challenging clinical problem. In broad terms, the occlusion may be embolic or thrombotic in origin and in over 90 per cent of cases it should be possible to make the distinction on clinical grounds at the initial presentation[21]. Where doubt continues concerning the precise diagnosis, arteriography remains the investigation of choice. The treatment of an embolic lesion should be by early embolectomy under local or general anaesthesia. If the occlusion is secondary to either arterial or graft thrombosis, the therapeutic approach is less clear[22–24].

The use of low-dose intra-arterial streptokinase[8,20,25,26] opens up an alternative therapeutic option in the management of high-risk patients with acute arterial occlusion. Fibrinolytic agents combined with percutaneous clot extraction and angioplasty[27] have been used successfully to treat underlying stenoses which may otherwise have required operative intervention. Prolonged infusions of low-dose fibrinolytic agents are associated wih systemic complications and should not be undertaken lightly[18,24,25]. Where lysis is likely to take

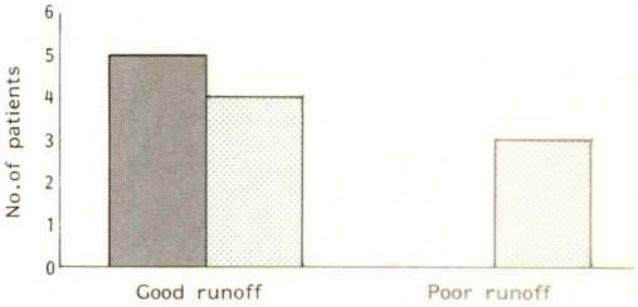

Figure 3 *Outcome of treatment related to run-off in group 2:* ■, *success;* ▨, *failure*

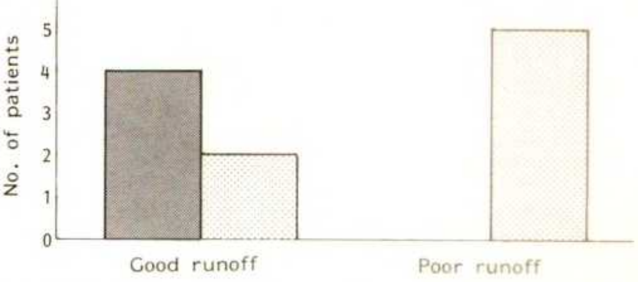

Figure 4 *Outcome of treatment related to run-off in group 3:* ■, *success;* ▨, *failure*

longer than 12 h, the infusion may be associated with a permanent neurological deficit despite a successful radiological result. The use of recombinant tissue plasminogen activator is a recent development which is reported to have fewer haemorrhagic side effects and better clot lysis than streptokinase. Despite its cost, it may well be the drug of choice in the future[19,28,29]. All these techniques require radiological expertise, very expensive equipment and vascular surgical support.

At present there is no consensus of opinion about which patients should be selected for treatment. Dotter *et al.* reported that streptokinase was ineffective in the presence of clot organization[3]. By contrast, several authors have demonstrated effective lysis in occlusions several months old[30–32]. Local thrombolytic therapy may well be the treatment of choice for chronic occlusion, as successful lytic therapy appears to be independent of the duration of symptoms[20–26]. Success rates are greater for occlusions of 10 cm or less and for iliac thromboses rather than for longer occlusions and smaller vessels[32].

The present results show that distal run-off is an important factor in successful streptokinase therapy. The better the run-off score, the greater the chance of lysis and long-term arterial patency, with or without the need for subsequent angioplasty or surgery. The practical difficulty with this observation is that preinfusion run-off cannot be assessed unless an earlier arteriogram is available. Newer techniques of distal vessel imaging may overcome this problem, namely the combined use of intra-arterial digital subtraction angiography with hyperaemia[33] and pulse generated run-off[34].

Streptokinase infusion is unhelpful for early graft occlusions (< 30 days) which are invariably due to poor selection and/or technical error. In these patients, surgery should be undertaken to correct the underlying problem if possible. Streptokinase should also be used with caution in patients with acute lower limb ischaemia following balloon angioplasty of iliac arteries, as unsuspected retroperitoneal haemorrhage carries significant morbidity and mortality rates. However, we recommend the use of intra-arterial streptokinase infusion in patients presenting with acute thrombotic occlusion in the presence of a good run-off and for those with late femorodistal graft occlusion.

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Consequences of radial and ulnar artery ligation following trauma

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It is widely accepted that ligation of either the radial or ulnar artery following trauma is generally tolerated without significant sequelae[1,2]. In spite of this, reports exist of attempted repair of these vessels[3,4]. It is known that vascular insufficiency can result from interruption of the radial artery for elevation of a radial forearm flap[5], following cannulation for monitoring[6,7], or following creation of an arteriovenous fistula[8]. These reports prompted an assessment of our policy of ligation of one or other forearm vessel following traumatic damage, in a situation where the hand is clinically well perfused.

Patients and methods

Of 649 consecutive patients undergoing surgery for wrist lacerations 36 had significant radial or ulnar artery damage. Arterial ligation was performed in 34 (94 per cent) patients because of the absence before operation of evidence of significant ischaemia of the hand as determined by clinical signs including an Allen's test[9]. Two patients (6 per cent) with ischaemia required arterial reconstruction. Of those who had had arterial ligation, 30 (88 per cent) were reviewed at a median period of 3·5 years (range 1–8·6 years) after operation, and these patients form our study population. The male:female ratio was 29:1 and median age was 25 years (range 4–75 years). The dominant hand was affected in 70 per cent of cases, and 80 per cent were manual workers. Glass lacerations accounted for 63 per cent. The radial artery was injured in 12 (40 per cent) cases and the ulnar in 18 (60 per cent). Isolated arterial injury occurred in five (17 per cent), the majority having associated nerve or tendon damage.

At review, clinical assessment was performed for evidence of arterial, nerve or tendon injury. Allen's test was performed on all wrist vessels: incomplete return of normal coloration to the pulp of the middle finger within 6 s of release of the compressed artery being taken as a positive result, indicating impaired blood supply[9]. An 8 MHz Doppler probe was used to detect pulsatile flow at the wrist and in the interdigital clefts. The unaffected hand was used as a control throughout.

Results

Eighteen patients (60 per cent) were asymptomatic but 12 (40 per cent) complained of cold hypersensitivity. This was severe in two cases, both of whom had an associated nerve injury. Of the symptomatic group 83 per cent had an associated nerve injury compared with 39 per cent of the asymptomatic group ($P < 0{\cdot}02$). In the asymptomatic group good recovery of nerve function had occurred in all cases, compared with only four of the ten symptomatic patients with nerve injury. Those with symptoms were also older (mean age 37 years) than those without symptoms (mean age 24 years) ($P = 0{\cdot}07$).

No patient had clinical signs of significant ischaemia. Allen's test on the uninjured forearm vessel failed to demonstrate impairment of blood supply in any case. Of the ligated arteries, Allen's test was positive in all. One ligated artery had a palpable pulse and Doppler flow was present in 15 (50 per cent) but these were obliterated by compression of the remaining patent wrist vessel, indicating flow to be of retrograde origin. In all cases Doppler demonstrated pulsatile flow in every interdigital cleft. In the normal hand the radial artery was palpable in all cases and the ulnar was palpable in 28 (93 per cent), the remaining two ulnar arteries having recordable Doppler flow. Allen's test was negative in 29 (97 per cent) of radial and 27 (90 per cent) of ulnar arteries.

Discussion

Although 40 per cent of our patients had symptoms compatible with vascular insufficiency, there was no evidence of impairment of blood supply and the weight of evidence suggests that these symptoms were caused by associated nerve injury. Our symptomatic group had a higher incidence of nerve injury than the asymptomatic group and also were older, a factor that adversely affects recovery of nerve function[10]. The adequacy of the remaining circulation to all the affected hands was confirmed by clinical means, including Allen's test and by detection of Doppler flow. This reinforces our belief that problems experienced by the symptomatic group were due to associated nerve injury, rather than to the effects of vascular ligation.

We conclude that ligation of either the radial or ulnar artery following trauma is not associated with any significant long-term ischaemic sequelae provided that clinical examination at the time of injury confirms the adequacy of circulation via the other wrist vessel. Adoption of such a policy will safely avoid unnecessary arterial repair in 95 per cent of radial and ulnar artery injuries.

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Angiographic embolization of intrahepatic arterioportal fistula

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Major arterioportal fistula is a rare curable cause of portal hypertension. It is usually acquired and is most frequently secondary to iatrogenic causes and trauma. In 1984 Malvy *et al.*[1] collected 21 cases from the literature and presented two additional reports of major persistent intrahepatic arterioportal fistulae complicating needle biopsy of the liver. The cases were treated conservatively and surgical treatment was reserved for complications of portal hypertension, especially bleeding oesophageal varices. Angiographic embolization has recently become an alternative to surgery, with acceptable immediate results[2–5], although it is uncertain whether revascularization may occur.

Case report

A 35-year-old woman presented with upper gastrointestinal haemorrhage in September 1989. Four years earlier, chronic active hepatitis (HbAg$^+$) had been diagnosed by percutaneous liver biopsy, the procedure being remembered as especially painful. She had no previous history of gastrointestinal bleeding, blood transfusion, alcoholism or drug addiction. Physical examination revealed moderate ascites and splenomegaly, although the blood biochemical determinations, coagulation studies and leucocyte and platelet counts were normal. Endoscopy showed large bleeding oesophageal varices which were successfully sclerosed. Ultrasonography demonstrated a central anechoic lesion in the right lobe of the liver which was interpreted as a cyst.

The patient rebled from oesophageal varices 1 month later and endoscopic variceal sclerotherapy was again successful. Portohepatic echo-Doppler examination revealed hepatofugal blood flow. Splanchnic and hepatic angiography (October 1989) demonstrated a hypertrophied and tortuous hepatic artery feeding a very active intrahepatic pseudoaneurysmal arterioportal fistula located centrally in the right lobe, with immediate retrograde filling of the portal vein (*Figure 1*) and reflux to the left gastric vein, with extensive collateral circulation through the oesophageal and perisplenic vascular beds. The fistula was embolized with four Gianturco (occluding string embolus, William Cook Europe, Denmark) coils. On control angiography 15 days later the fistula and its aneurysmic dilatations had disappeared (*Figure 2*), and there were fewer arteriographic signs of portal hypertension. Echo-Doppler examination showed hepatopetal portal blood flow. Percutaneous liver biopsy demonstrated chronic active hepatitis and portal fibrosis.

When the patient was reviewed 6 months later she was asymptomatic and routine analyses were normal. Endoscopy revealed less prominent oesophageal varices. Digital angiographic studies (April 1990) showed revascularization of the intrahepatic arterioportal fistulous sinus with filling of the portal vein in the early arterial phase and retrograde portal blood flow (*Figure 3*). Embolization was performed again with five Gianturco coils, almost eliminating the fistula, although some collateral vessels from the right hepatic artery or even from the left hepatic artery (which arose from the left gastric artery) bypassed the obstructive coils and still fed the fistulous area.

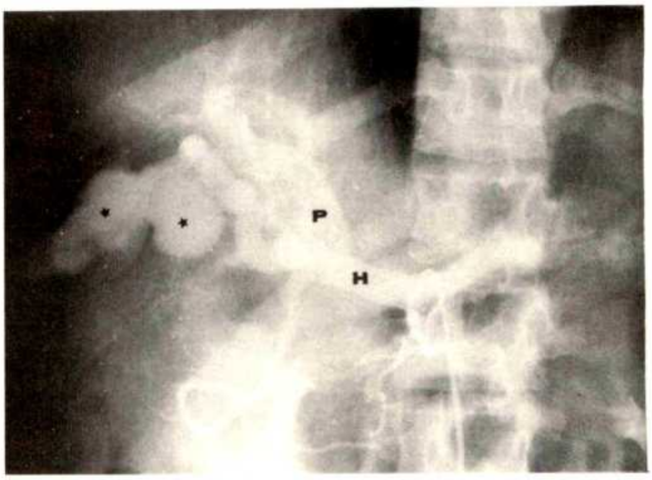

Figure 1 *Selective hepatic artery angiography showing a dilated, tortuous hepatic artery (H) feeding intrahepatic pseudoaneurysmal cavities (*) with immediate retrograde filling of the portal vein (P)*

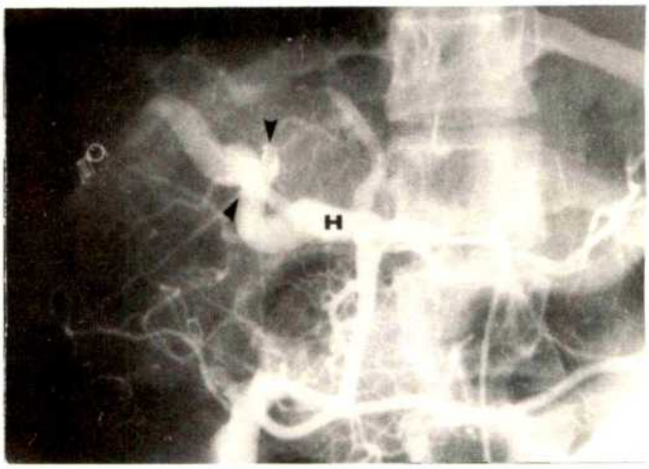

Figure 2 *Postembolization selective hepatic artery (H) angiography showing closure of the fistula, the arrows pointing to the obstructive coils, although the other two have migrated to the fistulous sinus. Note the improvement of blood flow through the gastroduodenal artery*

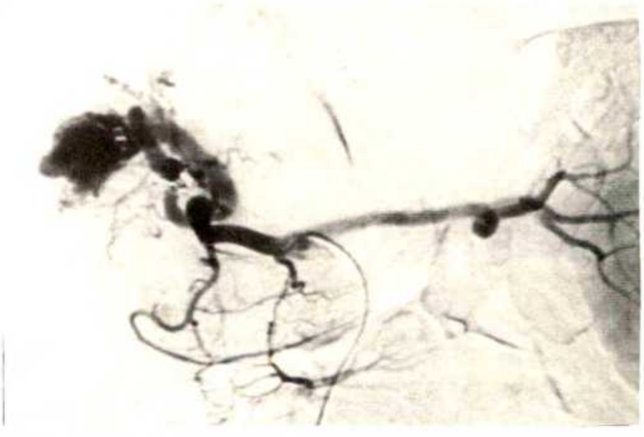

Figure 3 *Selective coeliac trunk digital angiography, 6 months after embolization, showing revascularization of the pseudoaneurysmal cavity with immediate retrograde filling of the portal vein. Note the bypassed coils*

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Discussion

Arterioportal fistulae produce hyperdynamic portal hypertension with its potential sequelae of variceal bleeding and ascites, and occasionally features of the mesenteric steal syndrome. When the fistula is within the hepatic parenchyma it may present particular pathological characteristics. Because hepatic artery and portal vein branches run parallel, penetrating iatrogenic or traumatic lesions can sever their walls and connect the two circulations through a complex intraparenchymatous pseudoaneurysm that grows, incorporating new vessels and occasionally biliary ductules[1,3,5], as in our patient. Surgical treatment of such fistulae has included ligation of the feeding artery, a direct transhepatic approach with endoaneurysmorraphy, or partial hepatectomy. Angiographic embolization of the intrahepatic fistula in our patient was successful, as in other reports[2–5], achieving closure and disappearance of portal hypertension. However, the fistula in our patient revascularized 6 months later from collaterals or even from the artery of the other hepatic lobe. Although further embolization closed the fistula, small vessels were still feeding it, suggesting that later recurrence was likely and indicating the need for a definitive surgical approach. Other authors have reported revascularization of intrahepatic fistulae after hepatic artery ligation[6] or after successful angiographic embolization[2,5].

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Surgical Research Society Abstracts

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The 73rd meeting of the Surgical Research Society, with Professor N. Browse in the Chair, was held at the Institute of Education, University of London on 3rd and 4th January 1991 and was organized by St Bartholomew's Hospital. Ninety-nine papers were presented during the scientific sessions which were preceded by a symposium entitled 'Shedding Light on Lasers'. The Patey prize was awarded to Ms I. M. Reid for her paper entitled 'Antitumour X Antilymphocyte Heteroconjugates Enhance Lymphocyte-Mediated Tumour Cell Lysis'.

Effect of basic fibroblast growth factor bFGF in a slow-release vehicle on incisional wound healing

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The pharmacological manipulation of wound repair is now a practical reality Basic FGF, a peptide with diverse effects on cells of mesenchymal origin, is potentially important in the control of healing Using a linear incisional skin wounding model, we have examined the effect of topical recombinant human bFGF on tensile strength. Male rats weighing between 350 and 500 g were used. Bilateral longitudinal paired dorsal incisions, 6 cm in length and 1·5 cm from the midline, were created One wound was treated with growth factor and the other acted as a control Six to eight rats were used for each variable. After killing, paired 1 cm strips were cut from both wounds simultaneously with a standard cutting instrument and tested to disruption on an Instrom tensiometer Two to three paired specimens were obtained per wound, statistical analyses are between paired strips. FGF in saline or collagen at a number of different doses failed to increase the strength of treated incisions and, at a dose of 50 μg/incision, actually decreased breaking loads in treated wounds compared to controls (201 (s.e.m 22) g cm^{-1} versus 287 (23) g cm^{-1} $p<0{\cdot}01$ Wilcoxon signed rank test) To delay the release of peptide within a wound, FGF was incorporated into red blood cell ghosts. Basic FGF in red blood cell ghosts at 5 μg/incision significantly increased the breaking load of treated wounds in comparison to control wounds at 7 days [390 (27) g cm^{-1} versus 256 (27) g cm^{-1} $p<0{\cdot}01$ Wilcoxon signed rank test]

The acceleration of healing by bFGF, contained only in a slow-release vehicle, suggests that its beneficial effects on fibroplasia may be mediated via a direct effect on fibroblast proliferation rather than augmentation of an inflammatory infiltrate.

Contraindication for one-stage proctocolectomy and pouch anal anastomosis in colitis

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Although there are reports of a successful outcome following pouch operations in patients with colonic Crohn's disease, it is now generally agreed that pouch–anal anastomosis is contraindicated in this disease. In patients without extra-colonic manifestations the pre-operative diagnosis of Crohn's disease has to be made by histological examination of mucosal biopsies taken at colonoscopy or rigid sigmoidoscopy

Between January 1985 and December 1989, 50 patients underwent colectomy (37) or proctocolectomy (13) for inflammatory bowel disease on the professorial surgical unit Each patient had undergone 1–5 episodes of endoscopic biopsy prior to operation

The pre-operative histological diagnosis was Crohn's disease in 13 patients, ulcerative colitis in 23 patients and non-specific (indeterminate) colitis in 14 patients Following operation, histological examination of the removed bowel confirmed the diagnosis of Crohn's disease in all 13 patients so diagnosed before operation However, 7 of the 23 patients (30·4 per cent) with a pre-operative diagnosis of ulcerative colitis and 4 of the 14 (28·6 per cent) patients with non-specific colitis were reclassified as having Crohn's disease.

In the absence of high quality frozen section histology at the time of colectomy, ileal pouches should only be constructed after preliminary colectomy has allowed exclusion of Crohn's disease

Primary systemic therapy for operable breast cancer

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Eighty-eight patients presenting with operable breast cancer of 4 cm or greater in diameter (T2, T3, N0, N1, M0) have received primary systemic therapy. Response was assessed following 12 weeks of systemic therapy by linear regression analysis of changes in tumour volume. Definitive locoregional surgery (mastectomy, $n=82$, wide local excision, $n=6$) was performed on completion of systemic therapy (3–6 months).

Response was observed in 24 (39 per cent) of the 61 patients who received endocrine therapy, all 24 had tumours with an oestrogen receptor (ER) concentration of ≥20 fmol mg^{-1} cytosol protein. Such patients had an excellent prognosis

Cytotoxic therapy was reserved for patients with tumours of ER concentration <20 fmol mg^{-1} cytosol protein ($n=27$) or when endocrine therapy had failed ($n=20$). Significant regression was observed in 34 patients (72 per cent), in 13 (27 per cent), complete clinical regresson was achieved. With a median follow-up period of 42 months (range 16–74 months), 23 patients have relapsed and 13 have died In 8 patients relapse was locoregional alone, 9 patients had distant metastasis alone, while 6 had both

This regime of primary systemic therapy allows selection of appropriate therapy. Survival compares very favourably to historical control population.

Ischaemia and reperfusion as a cause of leg swelling following femoropopliteal bypass

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Lower limb swelling after successful arterial reconstruction is common The role of oxygen-free radicals generated on reperfusion of ischaemic tissue, thromboxane generation and neutrophil activation has been investigated following femoro-popliteal bypass. Sixteen patients undergoing elective femoropopliteal (Fem-Pop) bypass and six patients undergoing varicose vein surgery were studied. Thromboxane levels (radio-immunoassay) and white cell activation (by flow cytometry) were measured in femoral venous blood prior to femoral clamping and at 5 min of reperfusion. Microvascular permeability was assessed in calf muscle biopsies prior to femoral clamping (pre) and on completion of bypass (post). Microvascular albumen leak was measured by fluorescein labelled monoclonal antibody to albumen

		TxB_2 (pg/ml)		PMN activation		Extravascular albumen	
Surgery	*n*	pre	5 min	pre	post	pre	post
Fem-Pop	16	84±22	764±98*	23±7	147±21*	3±1	51±12*
Varicose veins	6	89±19	98±27	12±4	16±4	3±1	2±1

* $p<0{\cdot}01$ between groups, ANOVA

Reperfusion following femoropopliteal bypass leads to a micro-

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vascular injury characterized by thromboxane production, white cell activation and increased microvascular permeability These are features typical of the ischaemic reperfusion injury which probably explains postoperative leg swelling.

Comparison of recombinant tissue plasminogen activator and streptokinase in peripheral arterial thrombolysis

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Limb salvage at 30 days is an acceptable criterion of outcome after peripheral arterial thrombolysis, but tends to overestimate efficacy due to limbs remaining viable but ischaemic, and also to limbs being salvaged by surgery. Therefore, in this study we have used the stricter criterion of 'limb salvage by lysis' to compare two different regimes. Cases of 149 patients having peripheral arterial thrombolysis were reviewed. Of these, 88 received streptokinase (SK) and 61 received recombinant tissue plasminogen activator (rt-PA) The two groups were not randomized but were selected according to the same criteria, over similar time periods and were well matched. The median time to lysis was significantly shorter in patients receiving rt-PA compared to those receiving SK (25 versus 40 h, $p<0{\cdot}0003$ Mann–Whitney) There was no significant difference in the incidence of haemorrhagic or other complications between the two groups.

		Outcome at 30 days			
Agent	Total no. of cases	Overall limb salvage	Amputation	Death	Limb salvage by lysis
SK	88	62 (70%)	18 (20%)	8 (9%)	38 (42%)
rt-PA	61	50 (82%)	3 (5%)	8 (13%)	38 (62%)
		n s	$p<0{\cdot}02$	n s	$p<0{\cdot}02$

The data presented suggest that rt-PA is a superior agent to SK in peripheral arterial thrombolysis

Role of fibroblasts in experimental liver metastasis

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Colorectal carcinomas commonly metastasize to the liver. In experimental models, healing and regenerating livers preferentially support metastastic growth[1] We studied growth factors and fibroblasts from regenerating livers and the effect of these fibroblasts in experimental tumour take

Regenerating rat livers were assessed for growth factor activity. epidermal growth factor (EGF) and fibroblast growth factor (FGF) were extracted by HPLC/heparin-Sepharose precipitation and measured using a bioassay of ^{125}I-UDR uptake. Additionally, regenerating and normal livers were disaggregated and cultured to obtain hepatic fibroblasts, quantified after 7 days Fibroblasts were then co-inoculated (10^5 cells) subcutaneously into nude mice with the human colorectal cell line HT29 (10^6). Resulting tumours were assessed after two weeks

There were two principal findings. Firstly, liver FGF levels peaked two days after partial hepatectomy (70 per cent increase over baseline, 495 ng). Secondly, cultures from regenerating livers yielded large numbers of proliferating fibroblasts ($38\times10^3/0{\cdot}5$ g liver), unlike untraumatized liver cultures ($0{\cdot}3\times10^3$, $p=0{\cdot}01$) These fibroblasts promoted 100 per cent HT29 tumour take in nude mice compared to controls (42 per cent, $p=0{\cdot}01$), the tumours were tenfold larger than controls.

Fibroblasts from regenerating livers promote tumour take and growth The events involved in this mechanism are likely to be crucial in hepatic metastases

1 Loizidou M, Lawrance R, Carty N, Cooper A, Alexander P, Taylor I. 1990 Macrophages and fibroblasts may enhance metastatic growth in the liver. *Gut* 30. 1498–99

Salivary epidermal growth factor and Barrett's columnar lined oesophagus

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Epidermal growth factor (EGF) is predominantly secreted in parotid saliva in man. The precise function of EGF is unknown, although it is a powerful mitogen for mucosal cells of the gastrointestinal tract and as such is implicated in renewal and repair mechanisms In animal models sialoadenectomy reduces ulcer healing and oral administration of EGF restores healing rates to normal. In man, patients with gastric ulcers and rheumatoid patients at increased risk of gastric ulceration, as well as those with resistant duodenal ulcers, have reduced salivary secretions of EGF when compared to age-matched normal controls. Barrett's columnar lined oesophagus (CLO) follows severe ulceration of the squamous lined oesophagus in patients with gastro-oesophageal reflux.

We investigated the possibility that patients with CLO had reduced oesophageal cytoprotection associated with low salivary EGF levels Of 180 patients studied, 56 patients with CLO were compared to 64 endoscopy normal controls Mean parotid salivary EGF concentration collected under standardized stimulated fasted conditions was 1300 ± 116 pg ml^{-1} in CLO patients compared to 2706 ± 500 pg ml^{-1} in controls, $p<0{\cdot}01$. EGF single parotid production was 1340 ± 110 pg min^{-1} (CLO) and 2200 ± 253 pg min^{-1} (controls) $p<0{\cdot}01$ Patients with malignant change in CLO ($n=15$) had concentrations and production EGF levels of 1340 ± 240 and 1280 ± 248 pg min^{-1} respectively (no difference to CLO alone).

Patients with Barrett's oesophagus have both low salivary EGF concentration and production which may contribute to the development of severe oesophageal damage

Stratified randomized prospective study of selective decontamination of the digestive tract

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Previous studies of selective decontamination of the digestive tract (SDD) have been criticized for design flaw, retrospective analysis of data and development of resistant microorganisms This study overcomes some of these objections by using a randomized, prospective, stratified design to evaluate the use of SDD (polymyxin, amphotericin tobramycin and i v cefotaxime) in reducing nosocomial infection, length of stay and mortality. A total of 331 patients admitted to an intensive care unit (ICU) were recruited over 18 months. with 256 patients remaining >48 h. Stratification by APACHE II preceded randomization to control (standard antibiotic therapy) or treatment (SDD) groups Patients were assessed twice daily for infection using a predetermined clinical scoring system, and on alternate days by APACHE II and sepsis score

	Total patients	Infected patients	Infection episodes	Mortality (%)	Mean stay (days)
Control	130	40	55	18·8	7·5
SDD	126	21*	25**	14·9	7·6

* $p=0{\cdot}01$, ** $p=0{\cdot}006$ χ^2 analysis

SDD significantly reduces nosocomial infection in ICU patients but does not reduce overall mortality or length of stay. Those patients with an APACHE II score range of 10–19 on admission showed the most significant reduction in infection (23/70 control versus 13/76 SDD, $p=0{\cdot}03$) and mortality (15/70 control versus 8/76 SDD, $p=0{\cdot}07$) Antibiotic usage was reduced in the SDD group These data support the use of SDD in selected ICU patients.

Outcome in patients with restorative proctocolectomy and a suspected diagnosis of Crohn's disease

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Restorative proctocolectomy was performed in 74 patients thought to have ulcerative colitis 14 are now considered to have Crohn's disease, despite the absence of small bowel disease, perianal disease and macroscopic evidence of ulcerative colitis. Crohn's disease was first suspected after resection in 6 of 10 patients who had a synchronous colectomy and pouch construction, hence a two-stage procedure might have reduced the risk of unidentified Crohn's disease In four patients having a two-stage procedure, only the protectomy specimen suggested Crohn's disease In the remaining four cases, Crohn's disease has only been suspected from pouch biopsies some years after resection Three patients developed pouch vaginal fistulas (two successfully treated) and three others have had pouch cutaneous fistula (one successfully treated, one pouch excised) One patient has had incapacitating diarrhoea (pouch excision). Half of these patients have satisfactory pouch function, but frequency is higher (7 per 24 h) than our colitic patients (5 per 24 h). The outcome of patients with Crohn's disease who have a pelvic pouch is not always unsatisfactory and at last half have a good outcome in the short term

Functional results and surgical complications in three pouch types

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Restorative proctocolectomy with ileal pouch–anal anastomosis is now well established treatment for ulcerative colitic (UC) and familial adenomatous polyposis (FAP) Various reservoir designs have evolved and this study compares the outcome of three major pouch types.

Between 1982 and 1990, 88 patients have undergone surgery Detailed analysis was performed on 61 patients (43 males, 18 females, median age 31 years, range 19–56), whose pouches had been functioning for at least 6 months. Fifty six patients had UC, four patients had FAP and one had severe constipation, J, S and W pouches were formed in 23, 15 and 23 patients, respectively The anal transition zone (ATZ) was preserved in 12 patients with J pouches, 17 with W pouches, but in none with an S pouch ($p<0{\cdot}005$)

There was no significant difference in individual surgical complications before or after ileostomy closure between the three groups. The hospital stay was, however, greater after construction of an S pouch ($p<0{\cdot}05$). Functional results showed that 52·2 per cent of patients with a J pouch required anti-diarrhoeals, compared to 6·7 per cent and 21·7 per cent with S and W pouches ($p=0{\cdot}05$) Only 7 (46·7 per cent) patients with S pouches could evacuate spontaneously, compared with 95·7 per cent of patients with a W pouch and all patients with a J pouch ($p<0{\cdot}001$). Bowel frequency was similar in the three groups Of the 61 patients, 48 (78·7 per cent) had perfect continence, 59 (96·7 per cent) had no urgency and 55 (90·2 per cent) were happy with pouch function. There was no difference in level of continence, degree of urgency or in the proportion of patients satisfied with the outcome, between the three groups. Twenty five of the 29 (86·2 per cent) patients who had ATZ preserved had perfect continence compared with 23 out of 32 (71·9 per cent) patients who had a complete mucosal proctectomy ($p=$ n s.)

In this study, W pouches appear to give the best overall functional result. There is also a trend towards better continence in patients with preservation of the ATZ

Prolonged and ambulant pH monitoring of the ileal pouch after restorative proctocolectomy

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The function of ileal pouches after restorative proctocolectomy remains unpredictable The role of pouch pH in determining pouch function has not been investigated To study the relationship between pouch pH and function, we have measured pouch pH in 17 ambulant patients following restorative proctocolectmy The indication for pouch construction was chronic ulcerative colitis in 12 patients and familial polyposis coli in 5 patients Eleven patients had a good functional outcome and 6 patients had a poor result. The total recording time was 20·5±6·5 h per subject (mean ±s.d.). The mean pH was 6·07±0·15 (mean ±s e m). There was a significant pH difference before and after pouch evacuation [pH 5·81±0·16 to 6·50±0·15, $p<0{\cdot}01$ (mean ±s.e.m.)] The mean pH after defaecation was significantly higher than the mean diurnal pH (pH 6·50±0·15 versus 6·08±0·16, $p<0{\cdot}01$). Patients with ulcerative colitis had a significantly lower pH than those with familial polyposis coli (pH 5·94±0·18 versus 6·37±0·24, $p<0{\cdot}05$)

The pouch pH did not show any correlation with meals, age, or sex. There were no diurnal differences in pouch pH during day or night

These data suggest that pouch pH may be an important factor in the regulation of pouch evacuation frequency after restorative proctocolectomy

Possibility of an immunological basis for pouchitis

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Pouchitis is a major long-term complication of restorative proctocolectomy with ileal pouch–anal anastomosis (IPAA). Few studies have documented its clinical associations.

Between 1982 and 1990, 88 patients underwent IPAA. Clinical data were analysed in 62 patients (44 males, 18 females), median age 31 years, range 19–56, whose pouches had been functioning for at least 6 months Fifty seven patients had ulcerative colitis (UC), four patients had familial adenomatous polyposis and one constipation. J, S and W pouches were formed in 23, 15 and 24 patients, respectively

Pouchitis occurred in 13 of 62 patients (20·9 per cent). There was no significant difference in its incidence between the three pouch types All of the patients who developed pouchitis had previously had UC. Nine out of the 13 patients (69·2 per cent) who developed pouchitis had one or more extra intestinal manifestations of UC prior to IPAA, compared to only 8 out of 44 patients (18·2 per cent) who did not develop pouchitis ($p<0{\cdot}005$*) (aphthous stomatitis = 8, iritis = 5, peripheral arthritis = 4, pyoderma gangrenosum = 2, sacro-iliitis = 1, ankylosing spondylitis = 1) Two of the 13 patients with pouchitis had an autoimmune disease (warm antibody autoimmune haemolytic anaemia and primary sclerosing cholangitis), compared to none in the non-pouchitis group ($p=0{\cdot}05$*). Pouchitis developed in 10 out of 46 (21·7 per cent) patients who hd total UC at the time of colectomy and in 3 out of 11 (27·3 per cent) who had more distal disease ($p=$n.s.*).

These findings could be considered as indirect evidence for the hypothesis that immune mechanisms play a role in the pathogenesis of pouchitis. Furthermore, they may have implications on the future selection of patients with UC for IPAA.

* Fishers exact test

Evaluation of two methods to assess the influence of calcium supplementation on ileo–anal pouch cytokinetics and function

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Frequency of defaecation following ileo–anal pouch construction bears a direct correlation to the ileal crypt cell production rate (CCPR) Calcium supplementation may improve pouch function by its antitropic effect which has been demonstrated in colonic mucosa, as well as its ability to chelate fat and bile The aim of this cross-over study was to determine whether oral calcium supplements (1·5 g calcium gluconate/day) or placebo administered for two months each, had an effect on frequency of defaecation following restorative proctocolectomy ($n=15$) and whether this was related to changes in CCPR assessed by an *in vitro* stathmokinetic and immunohistochemical (using monoclonal antibody Ki-67) methods

Calcium supplementation reduced the frequency of defaecation in nine patients during the day and eight patients at night ($p<0{\cdot}05$) Calcium also reduced CCPR from 3·5±1·3 to 1·9±1·0 cells crypt^{-1} h^{-1} ($p<0{\cdot}05$ paired t test) and caused a reduction in the crypt growth fraction (Ki-67) activity) from 23·1 per cent±8·2 to 12·7 per cent±3·1 ($p<0{\cdot}01$, Mann–Whitney).

This study suggests that calcium supplementation may improve pouch function by reducing the frequency of defaecation. This reduction is associated with significant changes in CCPR assessed by two techniques, suggesting that the mechanism is likely to be mediated by a direct effect on the ileal crypt cells, as well as a reduction in the luminal free bile and fatty acid load

Oral adsorbents and antibiotics as anti-endotoxin agents in experimental colitis

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Systemic endotoxaemia has been described in active inflammatory bowel disease and in an experimental model of colitis. Lactulose, a drug which can adsorb endotoxins and modify the gut flora, reduces systemic endotoxaemia in this model This study was undertaken to compare the efficacy of oral adsorbents and antibiotics as anti-endotoxin agents in experimental colitis

Colitis was induced in rats by intracolonic instillation of trinitrobenzenesulphonic acid and ethanol (TNBS/E). After 4 days the rats were treated with intragastric water, adsorbents (lactulose, kaolin or charcoal) or antibiotics (metronidazole and velosef, or neomycin) for 72 h Control rats received normal saline by intracolonic instillation Eight days after instillation, systemic blood was taken for endotoxin assay (quantitative limulus assay). A colon macroscopic score (CMS) was used to assess the severity of the TNBS/E induced colitis.

Treatment	Systemic endotoxin concentration (mean ± s.e.) (pg ml^{-1})	Colon macroscopic score (mean + s.e.)
Intracolonic TNBS/E		
Water ($n=15$)	39 8±12 6	4 2±0 6
Lactulose ($n=16$)	6 7±1 6$^+$	4 6±0 5*
Charcoal ($n=16$)	32·7±16·6*	4·4±0·6*
Kaolin ($n=16$)	5·3±2·1$^+$	4·4±0 6*
Metronidazole + velosef ($n=16$)	16·0±4·2*	3·1±0·5$^+$
Neomycin ($n=15$)	15 6±4 0*	5 0±0 3*
Intracolonic saline ($n=14$)	4 0±1·2$^+$	0·6±0 2$^+$

(Significance compared with water *n s., $^+p<0\ 05$, Mann–Whitney

Kaolin and lactulose therapy produced a significant reduction in systemic endotoxaemia. Oral metronidazole and velosef produced a significant improvement in the colon maxroscopic score without a significant reduction in systemic endotoxaemia Oral adsorbents are more effective than oral antibiotics in reducing systemic endotoxaemia in this model

Regulation of wound healing by T lymphocytes

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Large numbers of T lymphocytes are present in the healing wound. Lymphokines modulate macrophage and fibroblast function *in vitro*, but there is little information regarding the *in vivo* role of T lymphocytes in wound healing We therefore investigated the consequences of functional T lymphocyte depletion on the normal healing process Sixty male Lewis rats underwent a 7 cm dorsal skin incision with subcutaneous implantation of preweighed sterile polyvinyl alcohol sponges T lymphocytes were selectively depleted by intraperitoneal injection of 0 5 mg monoclonal antibody (mAb) on days −1, 3, and 7 The mouse anti-rat mAbs OX-19 (against all T), W3/25 (T helper) and OX-8 (T suppressor) were used. Matched controls received non-specific immunoglobulin. Ten days post-wounding healing was assessed by tensiometric measurement of fresh and formalin-fixed wound breaking strength Sponge hydroxyproline was determined as an index of reparative collagen synthesis T lymphocyte depletion in peripheral blood and wound was assessed by flow cytometry

	Wound breaking strength (g)				Hydroxyproline (μg/100 mg sponge)	
	Fresh		Fixed			
	Control	mAb	Control	mAb	Control	mAb
OX-19	243±16	196±11*	1033±45	820±50*	2315±125	1854±104*
W3/25	281±25	289±22	1035±71	1086±55	1588±62	1645±58
OX-8	240±15	295±16*	956±50	1108±51*	1539±54	1851±101*

*$p<0\ 05$, mean ± s e m

In conclusion, T lymphocytes enhance wound healing, since their depletion impairs all wound healing parameters. Depletion of T suppressor cells enhances wound healing suggesting a down regulatory role

Effect of gamma irradiation on isogeneic islet transplantation

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Islet pretreatment with gamma irradiation (2 5 Gy) has been shown to prolong allograft survival. The purpose of this investigation was to study the effect of irradiation (40, 20, 10 and 5 Gy) on islet viability Rat islets were isolated and cultured for 48 h before irradiation. Following 96 h further culture, 750 islets, found to be the minimum required to successfully reverse diabetes (blood glucose < 10 mmol l^{-1} by day 7), were transplanted to the renal subcapsular space of isogeneic streptozotocin-induced diabetic (BG > 20 mmol l^{-1}) recipients. Animals whose diabetes was reversed had an IVGTT (intravenous glucose tolerance test) at day 14 and the area under the IVGTT curve (AUC, area under curve) computed. In the 40 Gy group a reversal rate of 1/6 was observed This was significantly lower than that of the control group (8/8, $p<0\ 002$), and 20, 10 and 5 Gy groups (6/6 $p<0\ 008$) However, the AUC of the 20 Gy group was significantly higher than that of the control and 10 Gy groups ($p<0{\cdot}002$ in both). There was no significant difference between the AUC of the control and 10 Gy group Therefore, the maximum dose of gamma irradiation to which islets can be exposed without affecting function is 10 Gy This has important implications for human islet immunomodulation

Cyclosporine constricts arterioles in skeletal muscle

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Systemic hypertension following organ transplantation is associated with the administration of cyclosporine The mechanism of this hypertension is unknown, but it may involve a direct action of cyclosporine on peripheral arterioles We studied the responses to cyclosporine of the resistance (A1) and precapillary (A3–4) arterioles in skeletal muscle

The right cremaster muscle of decerebrated male Sprague–Dawley rats was dissected and stretched, with intact neurovascular connections, over an optical port in an environmentally controlled tissue bath Vessel diameters and red blood cell velocity were measured by *in vivo* video microscopy and optical Doppler velocimetry Measurements were taken at baseline, and following the addition of cyclosporine to the tissue bath (1·7 mM) ($n=5$) Control animals received either the cyclosporine vehicle ($n=5$) or saline ($n=5$) Cardiac output and blood pressure were measured by transpulmonary thermodilution and femoral cannulation The results are given in the *Table* as mean ±standard deviation

	Baseline			At 60 min		
	Saline	Vehicle	CSA	Saline	Vehicle	CSA
A1 diameter (μm)	122±13	121±9	118±8	122±11	120±15	67±10*
A3–4 diameter (μm)	17±2	18±3	18±3	17±2	18±5	4±6*
A1 flow (nl s^{-1})	280±95	282±80	248±63	287±65	252±90	89±28*

*$p<0\ 01$ from controls by ANOVA and Tukey-Kramer HSD CSA, cyclosporine

These results indicate that in this *in vivo* model, cyclosporine directly constricts A1 and A3–4 arterioles The locally activated vasoconstriction suggests involvement of a local mediator, or a direct action of cyclosporine on vascular smooth muscle This explains the increase in peripheral vascular resistance and systemic hypertension observed during cyclosporine administration

Reversibility of depressed immunity in cholestasis and the role of T cell subsets

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Cholestatic patients have a high incidence of infective complications which may partly be due to T lymphocyte suppression The role of T helper (TH) and T suppressor (TS) cells in this suppression is unknown. The speed at which T lymphocyte function returns after relief of biliary obstruction and the relative efficacy of internal and external biliary drainage in achieving this are unclear.

Rats were assigned to nine groups: controls, sham operated, bile duct ligation for 3 weeks, ligation for 3 weeks followed by internal drainage (ID) or external drainage (ED) for 1, 2 or 3 weeks. Peripheral blood T lymphocyte function was assessed by phytohaemagglutinin (PHA) stimulation. TH and TS cells were measured using monoclonal antibodies and flow cytometry Results are given in the *Table* as mean ±s e

Group	n	PHA (counts min^{-1})	TH/TS ratio
Control	11	5032±1140	2·13±0·20
Sham	11	4028±993	1·90±0·37
Ligated	11	1016±279*	1·87±0·25
Ligated, ID 1 week	8	1431±268*	2·10±0·28
Ligated, ID 2 weeks	8	1893±718*	1·69±0·26
Ligated, ID 3 weeks	8	2167±515	1·89±0·23
Ligated, ED 1 week	7	1080±271*	1·67±0·33
Ligated, ED 2 weeks	8	1479±379*	1·77±0·12
Ligated, ED 3 weeks	7	2573±1166	1·79±0·20

TH/TS ratio: no two groups differ, $p>0{\cdot}05$ ANOVA *Significant difference controls versus shams, $p<0{\cdot}05$ ANOVA

Suppression of T lymphocyte function in obstructive jaundice is not due to changes in TH/TS ratio. ID and ED are equally effective in reversing this suppression, but drainage for 3 weeks is required for return to control values

Graft tissues causing graft versus host disease in small bowel transplantation

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In contrast to other solid organ transplants, small bowel grafts carry a significant risk of graft versus host disease (GVHD) due to the large number of T cells in the mesenteric lymph nodes (MLN), Peyer's patches and lamina propria The aim of this study was to assess the effect of excision of MLN on the development of GVHD in rat small bowel transplantation.

Transplantation was carried out from parent to F1 hybrid rat strains; this model usually results in fatal GVHD with no concomitant rejection. Six animals were studied in each group. The groups were as follows· group A, PVG to PVGxDA, group B PVG to PVGxDA+removal of graft MLN, group C DA to PVGxDA and group D DA to PVGxDA+removal of graft MLN The strains were chosen from the results of previous work which suggested that transplantation from PVG to PVGxDA represents a strong model for GVHD and from DA to PVGxDA a relatively weak model. Following transplantation, development of GVHD was measured and survival recorded.

Group	Strain combination	Removal of MLN	GVHD	Survival (days)
A	PVG to PVGxDA	–	+	17,17,19,21,21,22
B	PVG to PVGxDA	+	+	20,22,23,23,23,25
C	DA to PVGxDA	–	+	30,32,33,34,>40, >40
D	DA to PVGxDA	+	–	>150 in all

Survival, A versus C $p<0{\cdot}01$, B versus D $p<0{\cdot}01$ by Wilcoxon rank sum test

In the first three groups, histological changes of GVHD were found in host bowel In the group which survived >150 days there were no histological signs of GVHD. We conclude that in small bowel transplantation GVHD can occur despite removal of graft MLN. This implies that in clinical small bowel transplantation efforts to prevent GVHD must be directed at lymphocytes in the mucosa and Peyer's patches as well as in the MLN

Human reconstituted severe combined immunodeficient mouse – a model for isogeneic and allogeneic human islet transplantation

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The purpose of this study was to develop an *in vivo* model for assessing human islet allograft survival Severe combined immunodeficient (SCID) mice were reconstituted with a human immune system by the intraperitoneal injection of 5×10^7 splenocytes (prepared from organ donor spleens). Ten days after reconstitution, the mice had high levels of human immunoglobulin in their sera and responded to a tetanus toxoid injection with the production of human anti-tetanus toxoid IgG Analysis of the reconstituted SCID spleens showed numerous T cell areas (CD3 positive) and follicles containing B cells (CD19 positive). The model of isogeneic transplantation was provided by reconstituting with splenocytes from an organ donor and transplanting islets from the same donor to the renal subcapsular space The model of allogeneic human islet transplantation was provided by splenic reconstitution followed by transplantation with islets from an unrelated donor

We found that isogeneic transplants were accepted with no evidence of rejection Allogeneic transplants, however, were rejected, and immunohistology showed that the infiltrating cells were of human lymphoid origin The majority of these cells were T cells (CD3 positive), of which 80 per cent were cytotoxic effector cells (CD8 positive) and the remainder were CD4 positive helper T cells. In conclusion, the human reconstituted SCID mouse provides an excellent model system in which to study human islet immunogeneicity and is potentially of great value for assessing the efficacy of islet immunomodulation protocols

Neutrophil adherence receptors (CD18) in lung injury following lower limb ischaemia

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Reperfusion of the lower limbs following aortic surgery leads to lung injury mediated by activated neutrophils (PMN). *In vitro*, PMN require adhesion to endothelium to induce permeability CD18, a receptor for PMN adherence, was studied in a model of lung injury following lower limb ischaemia

Anaesthetized rabbits treated with saline ($n=9$) or a monoclonal antibody to CD18 ($n=10$) underwent 3 h of bilateral hindlimb ischaemia or a sham procedure ($n=11$) Circulating white blood cells (WBC) were counted 10 min after tourniquet release After 4 h, quantitative histology, bronchoalveolar lavage and calculation of lung wet/dry weight ratio were performed on excised lungs

	$10^{-9} \times$ WBC per l	PMN	Lavage protein (μg ml^{-1})	Wet/dry ratio
Sham	6·07±0·61	31±3	277±46	4·29±0·21
I/R (saline)	3·56±0·49*	52±4*	554±90*	5·10±0·10*
I/R (CD18 antibody)	7·29±1·05*	$34\pm3^{+}$	324±41	$4{\cdot}61\pm0{\cdot}10^{+}$

$p<0{\cdot}05$. *compared with sham, $^{+}$compared with I/R (saline) The number of PMN is given per ten high power fields. I/R, ischaemia/reperfusion

In ischaemic and reperfused animals treated with saline, there was leucopenia, neutrophils were sequestered in the lungs and there was permeability and oedema, indicated by bronchoalveolar lavage protein and wet/dry weight ratio The CD18 antibody prevented the leucopenia and the adherence of activated PMN in the lungs.

Permeability and oedema was reduced. The antibody did not induce leucocytosis in shams The CD18 adherence receptor appears to be important in mediating the PMN-dependent lung injury following bilateral hind limb ischaemia

Effect of pulmonary intravascular macrophages on lung injury induced by remote ischaemia

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Intravascular macrophages in the lungs may localize mediators of remote injury to the lung. Chronic lung lymph fistulae and central pressure lines were inserted in 23 anaesthetized sheep before 2 h of bilateral hindlimb tourniquet ischaemia and reperfusion for 4 h. Pulmonary intravascular macrophages (PIM) were inactivated by an infusion of dinitrodibenzoate-enriched liposomes in eight animals three days prior to the ischaemia Controls underwent PIM inactivation without ischaemia ($n=4$) or blank liposome administration and ischaemia ($n=4$). Pulmonary artery pressure, plasma thromboxane, lung lymph thromboxane and protein clearance were measured.

PIM	Ischaemia	Pulmonary artery pressure mmHg (reperfusion 5 min)	Thromboxane (pg ml⁻) Plasma (reperfusion 5 min)	Thromboxane (pg ml⁻) Lung lymph (reperfusion 120 min)	Protein clearance (mg/30 min) (reperfusion 120 min)
+	+	38±9*	735±94*	1700±110*	5·1±0·9*
−	+	36±7*	814±81*	398±81	2·4±0·2
−	−	13±3	190±58	414±64	2·3±0·2
+	−	12±4	211±64	437±77	2·5±0·3

*$p<0.05$ relative to baseline ANOVA

Lower limb ischaemia and reperfusion produced a rapid rise in pulmonary artery pressure and plasma thromboxane with subsequent increases in microvascular permeability The elimination of PIM prior to ischaemia and reperfusion reduced these measures of lung injury.

These results suggest that intravascular macrophages may be responsible for localizing mediators of a remote insult to the lung and amplifying the resulting injury.

Effect of phalloidin and antamanide on lung injury following interleukin 2

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The dose of interleukin 2 (IL-2) in tumour immunotherapy is limited by oedema which may be due to alterations in the endothelial cell cytoskeleton. The *Amanita phalloides* derivatives, phalloidin and antamanide, may assemble cytoskeletal microfilaments and their effect on oedema produced by IL-2 *in vivo* was evaluated.

Anaesthetized rats were treated at 30 min periods with saline ($n=36$), phalloidin ($n=21$), or antamanide ($n=21$), starting 30 min prior to the 1 hour infusion of 1×10^6 U recombinant human IL-2 or saline. After 6 h, the wet/dry weight ratio was estimated for oedema, bronchoalveolar lavage was performed for protein leak, and quantitative lung histology was recorded

	Wet/dry ratio	Lavage protein (μg ml^{-1})	PMN
Control	3·94±0·20	458±84	21±2
IL-2 (saline)	4·75±0·14*	1770±260*	49±6*
IL-2 (phalloidin)	4·47±0·07⁺	955±200⁺	37±5*
IL-2 (antamanide)	4·39±0·12⁺	482±13⁺	49±5*

*$p<0.05$ compared to control; $^+p<0.05$ compared to IL-2 (saline). PMN, number of neutrophils per 10 high power fields

IL-2 infusion led to oedema, protein leak and neutrophil sequestration in the lungs. Phalloidin and antamanide reduced oedema and permeability but did not significantly affect neutrophil sequestration in the lungs. These data suggest that oedema and permeability caused by IL-2 may be modulated by the endothelial cytoskeleton

Ischaemia/reperfusion injury to the rat kidney: protection with single dose sodium bicarbonate

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Toxic levels of endogenous ammonia have been demonstrated in the kidney following ischaemia Urinary alkalinzation by inhibition of the renal ammonia-producing glutaminase system may protect against postischaemic renal injury[1].

To test this hypothesis, three groups of 10 male Wistar rats weighing 250±50 g were treated intravenously as follows 3 h prior to 90 min of warm unilateral renal renal ischaemia group 1, 1 ml 8·4 per cent sodium bicarbonate; group 2, 1 ml normal saline, and group 3, 2 ml 3 per cent saline Groups 1 and 3 received identical quantities of sodium Contralateral nephrectomy was performed at the onset of ischaemia. Serum creatinine levels were measured pre-operatively and on days 1, 3 and 7 postischaemia. The kidneys were then taken for histology

Results indicate that renal function was significantly protected in group 1, creatinine levels rising to a maximum of 444±31 μmol l^{-1} on the third day postoperatively compared with 953±19 μmol l^{-1} in group 2 and 948±16 μmol l^{-1} in group 3 ($p<0.001$, Student's *t* test). By the seventh postoperative day there was 70 per cent survival in group 1 (and normal serum creatinine levels), compared with zero survival in groups 2 and 3, all of whom died on the third postoperative day. Histology of control and treated kidneys showed the characteristic red cell packing of peritubular capillaries in the cortico-medullary junction present in the control animals but not in group 1

Ischaemia/reperfusion injury to the rat kidney is prevented by intravenous administration of 8·4 per cent sodium bicarbonate prior to surgery The protective action is due to the bicarbonate component.

1 Fitzpatrick JM, Wickham JEA Renal accumulation of ammonia· The cause of post-ischaemic functional loss and the blue line *Br J Urol* 1982; 4· 602–12.

Neutrophils migrating to the alveolus exhibit enhanced oxidant generation in lung injury

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Toxic oxidants generated by neutrophils (PMN) migrating into the alveolus in sepsis-induced acute lung injury have been implicated in host tissue damage. To study this phenomenon, release of the superoxide anion (O_2^-, cytochrome *c* reduction, $n=6$) and hypochlorous acid (HOCl, 5-thio-2-nitrobenzoic acid oxidation, $n=5$) from PMN, isolated from both vascular (0, 60 and 300 min) and alveolar spaces (300 min) was assessed in septic swine. Young pigs (10–20 kg) were anaesthetized and ventilated (F_{IO_2} 0·5, PEEP 5 cm H_2O) and received a 1 h infusion of 0·9 per cent NaCl (controls) or live *Pseudomonas aeruginosa* (5×10^8 c f u ml^{-1} at 0·3 ml 20 kg^{-1} min^{-1}) Controls did not demonstrate enhancement of PMN oxidant release and alveolar-capillary membrane permeability as assessed by bronchoalveolar lavage protein and extravascular lung water accumulation was unchanged

Results shown in the *Table* indicate that alveolar PMN from *P. aeruginosa*-treated animals produced significantly greater quantities of O_2^- and HOCl than vascular PMN at 0 min and this was associated with significantly increased bronchoalveolar lavage protein and extravascular lung water ($p<0.05$).

	P aeruginosa-treated PMN 0 min	60 min	300 min	Alveolar
O_2^- (nmol/min)	1·6±0·2	2·1±0·1*†	5·0±0·4*	3·6±0·4*
HOCl (nmol/20 min)	7·7±0·6	9·6±0·5*†	12·9±0·4*	14·4±1·2*

*$p<0.05$ versus 0 min, †$p<0.01$ versus 300 min; Student's *t* test

Neutrophils migrating into the airspace in septic acute lung injury exhibit an enhanced oxidant burst and thus have the potential to effect alveolar capillary membrane injury.

Effect of lipid components of total parenteral nutrition regimens on lymphocyte activation via the phosphatidylcholine:lipid ratio

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The lipid component of total parenteral nutrition regimens has been shown to be responsible for suppression of the activation of human lymphocytes, both *in vitro* and *in vivo*.

In order to determine the possible causes of this immunosuppression, commercially available lipid solutions and individual solution components were assayed for suppressive activity These components include lipid (triglycerides/fatty acids), phosphatidylcholine (PC) and glycerol in water. Healthy human peripheral blood lymphocytes were incubated with the test solution and interleukin 2 (IL-2, 1000 U ml^{-1}) for 4 days prior to evaluation of cytotoxicity by chromium release assay. The results are summarized in the *Table*

Solution	PC.lipid ratio	Inhibition of cytotoxicity (%)	
Intralipid 10%	1 2.1	68	at 1 mg ml^{-1} lipid
Intralipid 20%	0·6 1	48	
Lipofundin S*	0 75:1	78	
Lipofundin M/L	0 6·1	32	
Glycerol		None	at equivalent doses to above
Egg phosphatidylcholine		37	
Soya phosphatidylcholine		74	

* Contains soya PC, other solutions contain egg PC

These data reveal that the relative composition of lipid solutions may influence their immunosuppressive activity Emulsifying agents such as PC may be immunologically detrimental to patients receiving total parenteral nutrition, possibly due to effects on lymphocyte cell membrane structure and function.

Anal intraepithelial neoplasia in HIV-seropositive men

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A study of patients with anal condylomata by Scholefield *et al* [1] showed a prevalence of anal dysplasia (AIN) of 28 per cent. There was a highly significant difference in prevalence between heterosexual and homosexual men and an indication that the prevalence was highest in HIV-seropositive patients.

This study has assessed the prevalence of AIN in a group of HIV-seropositive men with and without anal condylomata using micro-anoscopy and biopsy Of 48 HIV-seropositive patients, all of whom were homosexual or bisexual, 29 had anal condylomata at the time of examination, 13 of these also showed histological evidence of AIN. Only 3 of the group of 19 without anal condylomata showed histological evicence of AIN. The difference in prevalence of AIN between the group with and the group without anal condylomata was statistically significant ($p=0\ 012$, Fisher's exact test).

In conclusion we have shown a high prevalence of AIN in HIV-seropositive men and confirmed that AIN is asociated with the presence of anal condylomata

1 Scholefield JH, Sonnex C, Talbot IC, Palmer JG, Whatrup C, Mindel A, Northover JMA Anal and cervical intraepithelial neoplasia possible parallel *Lancet* 1989; ii· 765–9.

Adhesion prophylaxis with tissue plasminogen activator

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A unifying hypothesis states that peritoneal fibrinolytic activity is reduced in conditions associated with adhesion formation. Using a functional assay of plasminogen activating activity (PAA), we have examined the time course of changes in peritoneal fibronolysis following ischaemia and have attempted to prevent adhesion formation using recombinant tissue plasminogen activator (rtPA) incorporated in a carrier gel

Seventy male Wistar rats were randomized to either sham laparotomy or ischaemic peritoneum (six ligated buttons of peritoneum giving a quantitative adhesion score of 0–6). Peritoneal biopsies were obtained from five animals in each group at seven time intervals and assayed for PAA Compared with sham laparotomy, ischaemia resulted in adhesion formation in all animals and a significant reduction in PAA in the first 24 h (median 0 112 IU cm^{-2} versus 0 05 IU cm^{-2}, $p<0\ 01$, ANOVA).

Ischaemic buttons were produced in 36 rats and the animals randomized to no treatment, gel alone or rtPA-gel. At one week, rtPA-treated animals formed significantly fewer adhesions compared with gel alone or controls (median number of adhesions 1 5 versus 3 versus 5, $p<0{\cdot}001$, ANOVA)

These studies indicate that reduced fibrinolytic activity associated with ischaemic adhesion formation is maximal in the first 24 h Local rtPA delivered in this period is able to reduce the formation of adhesions and has potential for clinical application

Effect of transforming growth factor beta (TGF-b) on steroid impairment of intestinal wound healing

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A number of peptide growth factors are implicated in the control of wound healing Pharmacological doses of these proteins can be shown to alter various parameters by which we evaluate wound repair in healing incisional skin wounds. Wound failure in the intestine is more serious and particularly common in situations where healing is impaired We have previously demonstrated impairment of healing pig enterotomy wounds by betamethasone 12 mg/50 kg i m bd We have now assessed the effect of local applications of two peptides, recombinant human basic fibroblast growth factor (bFGF, 5 μg per incision) and bovine transforming growth factor beta (TGF-b, 5 μg per incision) in steroid-impaired animals.

Nineteen steroid-treated landrace pigs weighing between 18 and 25 kg underwent laparotomy. At operation, paired longitudinal enterotomy wounds (each of a pair was 30 cm from its partner) were constructed at four sites, three in the terminal ileum, one in the right colon. Into each of a pair at the time of surgery was placed either growth factor in a collagen suspension or a collagen suspension alone. Healing was assessed at 7 days by the measurement of breaking load. Paired wounds were compared statistically. FGF, 5 μg per incision, decreased ileal breaking loads (mean 143 g cm^{-1}, s e.m. 19, versus 198 g cm^{-1}, s e.m. 21, $n=12$ pairs, $p<0{\cdot}05$, Wilcoxon signed rank test) TGF-b increased breaking loads of both ileal (285 g cm^{-1}, s.e.m 32, versus 167 g cm^{-1}, s e.m 12, $n=18$ pairs, $p<0\ 05$ Wilcoxon signed rank test) and colonic (363 g cm^{-1}, s.e m 66 versus 262 g cm^{-1}, s.e.m. 45, $n=6$ pairs) wounds almost to the levels seen in non-steroid-treated animals There were no significant differences in breaking load between paired wounds treated with collagen vehicle alone or saline

A local application of TGF-b in a collagen suspension reverses the deleterious effects of steroid therapy on intestinal wound breaking strength.

Effect of antitumour × anti-lymphocyte heteroconjugates on lymphocyte-mediated tumour cell lysis

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The covalent bonding of an anti-tumour antibody specific for tumour cell surface antigen with an anti-lymphocyte antibody specific for the T-lymphocyte receptor complex, produces a heteroconjugated antibody that can activate and redirect cytotoxic T-lymphocytes to lyse tumour cells We tested the ability of the antitumour × antilymphocyte heteroconjugate 96 5 × 500A2 to lyse murine melanoma K1735 cells *in vitro* in a 4-h chromium release assay using cultured murine splenocytes, and *in vivo* with a neutralization assay in C3H/HeN mice.

When cultured splenocytes were incubated with target cells at an effector·target ratio of 25·1, the mean percentage specific lysis (±s e) was 4 1±2·19 per cent. The addition of heteroconjugate significantly increased lysis to 78 4±3 81 per cent ($p<0{\cdot}01$).

In an initial *in vivo* model, mice received 1×10^5 tumour cells by intravenous injection followed by RPMI medium (controls) or splenocytes plus heteroconjugates (treatment). Pulmonary metastases were measured on day 14. The mean number of pulmonary metastases (±s.e.) in the control group was 231±19, compared to 22±3 in the treatment group ($p<0\cdot05$).

Antitumour × antilymphocyte heteroconjugates can retarget splenocytes to lyse tumour cells *in vitro* and can reduce pulmonary metastases after intravenous tumour injection. Studies to further assess the *in vivo* efficacy of heteroconjugated antibodies are in progress.

Technetium-99m renography screening of renal artery stenosis in hypertensive patients with peripheral vascular disease

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Atherosclerotic renal artery stenosis (RAS) is a recognized cause of hypertension which may occur in association with peripheral vascular disease. Pre-operative imaging of the renal vasculature facilitates simultaneous renal artery reconstruction during aortic surgery. The results of technetium renography were compared with arteriography to determine whether this is a satisfactory test for the detection of RAS.

Seventy two hypertensive patients were prospectively studied before aortic reconstructive surgery. All were investigated by selective renal arteriography and by quantitative isotope renography. These tests were assessed blind and all arteriograms were graded by a single radiologist.

RAS was detected by arteriography in 35 patients (49 per cent); 24 (33 per cent) had mild stenosis, 7 (10 per cent) had moderate stenosis and 4 (6 per cent) had severe stenosis. Of these 35 patients, only 8 (11 per cent) were correctly identified by isotope renography. None of the four with severe stenosis was identified. Isotope renography resulted in 8 true positives and 6 false positives with 31 true negatives and 27 false negatives.

We conclude that isotope renography does not fulfil the criteria for a screening test for the detection of RAS and appears to be of no value in those patients undergoing aortic surgery in whom selective renal arteriography may not be indicated.

Correlation of expression of the oestrogen-regulated protein pS2 with good short term prognosis in breast cancer

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pS2 is an 84-amino-acid cysteine-rich protein of unknown function. Expression of the pS2 gene messenger ribonucleic acid (mRNA) occurs in response to oestrogenic stimulus and coincides with oestrogen/receptor complexes appearing in the nucleus of breast cancer cells. The aim of this study was to determine whether tumour pS2 expression was related to disease behaviour. RNA was extracted from snap-frozen tumour tissue from 80 consecutive patients. Tumour RNA (20 μg) was denatured, subjected to electrophoresis, Northern blots incubated with a radiolabelled pS2 probe and the pS2 mRNA detected by autoradiography. The Northern blots were reprobed with actin control and pS2 expression quantified by densitometry. All patients were meticulously followed both clinically and radiologically.

pS2 mRNA was expressed in 25 of the 78 assessable tumours. With minimum follow-up of 24 months, pS2 mRNA expression significantly correlated with freedom from early disease recurrence (see *Table*; $p=0\cdot015$, Fisher's exact test). Furthermore, tumour oestrogen receptor protein content achieved no such correlation.

	pS2 mRNA expression	
	Nil detected	Present
Disease recurrence	14	1
Disease-free	39	24

These data suggest that tumour expression of the oestrogen-regulated gene pS2 delineates a subgroup of patients likely to remain disease free at short-term follow-up.

Duplex sonography: a novel method of detecting colorectal liver metastases

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Conventional imaging techniques are of limited value in detecting small liver metastases. Previous studies using an indirect method of assessing blood flow (hepatic perfusion index) have shown that metastases may be associated with subtle changes in liver blood flow[1]. Unfortunately, doubts have been expressed about its reliability. Doppler ultrasonography, however, has the ability to measure blood flow directly. The aim of this study was to evaluate duplex sonography as a method of detecting liver metastases.

Hepatic arterial and portal venous blood flow was measured in 30 patients awaiting surgery for colorectal cancer, and in 16 healthy volunteers. The ratio of hepatic arterial to total liver blood flow (doppler perfusion index, DPI) and the ratio of hepatic arterial to portal venous blood flow (dopper flow ratio, DFR) were calculated (mean±s.d.).

	Controls ($n=16$)	Overt liver metastases ($n=19$)	Disease-free liver laparotomy ($n=11$)
DPI	0·13±0·07	0·52±0·13	0·39±0·17
DFR	0·15±0·09	1·23±0·61	0·71±0·46

Clear separation of the DPI and DFR values of controls and patients with histologically confirmed hepatic metastases were observed ($p<0\cdot001$).

The data suggest that the measurement of liver blood flow by duplex sonography may be of value in the diagnosis of colorectal liver metastases.

1. Leveson SH, Wiggins PA, Giles GR *et al.* Deranged liver blood-flow patterns in the detection of liver metastases. *Br J Surg* 1985; 72: 128–30.

Videoproctographic studies suggest that an anterior repair may be the optimum surgical treatment of neuropathic faecal incontinence

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The impact of three types of pelvic floor repair have been evaluated by videoproctography: postanal repair (PAR, $n=34$), anterior levatoplasty and sphincter plication (AL, $n=7$) and total pelvic floor repair (TPFR, $n=17$). Parameters measured include: length of anal canal, anorectal angle, perineal descent and pelvic floor descent at rest, during maximum squeeze effort and on straining, rectal evacuation, rectocoele, funnel deformity and pelvic floor movements.

PAR resulted in an increase in anal length (3·4–3·7 cm) but there was no change in anorectal angle, incidence of rectocoele, or funnel deformity. Furthermore, perineal descent at rest and pelvic floor movements deteriorated. TPFR resulted in no change in anal canal length or angles, but funnel deformity fell from 76 to 58 per cent, as did the incidence of rectocoele (82 to 52 per cent). Despite this, pelvic floor position, perineal descent and pelvic floor movements deteriorated after operation. Only after AL was there a lengthening of the anal canal (3·3–4·0 cm), a reduction in perineal descent (7·6 to 6·9) and pelvic floor position (5·0 to 4·0), an increase in pelvic floor movement (0·3 to 0·6) and correction of a rectocoele (86 to 29 per cent). These data suggest that anterior levatoplasty and sphincter plication may be the optimum treatment of faecal incontinence.

Characterization of sphincter injury following anal dilatation

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Anal dilatation is still used in the treatment of anal fissure and haemorrhoids despite several reports of faecal incontinence following this operation. We have used anorectal physiology and anal ultrasound in an attempt to study the function and structure of the anal sphincter in patients rendered incontinent by this procedure

Twelve male patients (mean age 50·5 years) with faecal incontinence following anal stretch underwent measurement of resting and contraction pressures, anal canal length and pudendal nerve latencies Patients with a history of other perianal surgery were excluded. Anal endosonography was then performed

Resting pressure, reflecting internal anal sphincter function, (mean ± s e.m , 49 ± 3 cmH_2O) was lower than normal (60 cmH_2O), but the mean contraction pressure was normal (93 ± 13 cmH_2O). Anal canal length was normal (3·3 cm) and all patients had normal pudendal nerve latencies

The results of anal endosonography showed that the internal anal sphincter was disrupted in 11/12 patients, with a mean loss of 6·9 h Rather than a single break, the internal anal sphincter was disrupted in several places in 10 patients. Three patients also showed defects of the external sphincter. One patient had a normal endosonographic appearance

This study has, for the first time, demonstrated the effect of anal dilatation on the structure of the anal sphincter muscles. In these patients, anal dilatation caused rupture and fragmentation of the internal anal sphincter In a proportion, the striated muscle was also disrupted. The delicate anal sphincter mechanism is vulnerable to uncontrolled stretching

Prediction of anorectal trauma from delivery variables

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Childbirth results in a temporary but significant reduction in resting (MRP) and voluntary contraction (MVC) anal pressures, and reduced anal sensitivity To determine the role of baby weight, head circumference, total length of second stage, and length of active second stage, we measured anal pressures, mucosal electrosensitivity, puborectalis and external sphincter fibre density, and pudendal nerve terminal motor latency in 125 primiparous women MRP was significantly reduced immediately postnatally [50 cmH_2O (10–115) versus 70 (50–125); p<0·001] but this did not correlate with baby weight (Rs* = −0·2522), head circumference (Rs = −0·1763), total length of second stage (Rs = −0·1628), length of active second stage (Rs = −0·1867). Similar findings were seen with regard to MVC Pudendal nerve terminal motor latency remained increased 6 months postnatally [antenatal 1·8 ms (1·4–2·3) versus postnatal 1·8 ms (1·2–3); p=0·01] but did not correlate with baby weight, head circumference, total length of second stage or length of active second stage Puborectalis and external sphincter fibre densities were not significantly altered by delivery compared to antenatal values The anal canal mucosal electrosensitivity of the upper anal canal was impaired by delivery [antenatal 4·25 mA (1·8–10) versus postnatal 6·05 (1·9–26); p<0·05] but this did not correlate with baby weight (Rs = 0·1091), head circumference (Rs = 0·1251), total length of second stage (Rs = 0·1571) or length of active second stage (Rs = 0·1637).

We conclude that neither baby size, nor the length of second stage labour, or the time spent actively pushing, influenced the extent of anorectal trauma.

* Spearman ranked correlation

Relationship between intussusception in constipated patients and the anorectal angle

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We investigated the relationship between the anorectal angle and the presence of a rectocoele or intussusception in 110 constipated patients and 30 healthy controls. Anorectal angles were measured radiographically in the left lateral position at rest, during squeezing and straining. Abnormalities in rectal wall configuration were identified during proctography.

Rectocoeles, defined as a bulge of the anterior rectal wall > 2 cm, occurred in 22 patients Intussusception, defined as invagination of the rectal wall during straining occurred in 26 patients Both abnormalities were found in 12 patients and no radiological abnormality was present in 50 patients.

	n	Rest	Squeeze	Strain
Control	30	84(6)	78(7)	99(1)
Constipated	110	92(2)	81(2)	105(2)
No abnormality	50	86(2)	77(2)	100(3)
Rectocoele	22	88(4)	78(4)	98(4)
Intussusception	26	102(3)	88(3)	118(4)
Both abnormalities	12	100(5)	87(5)	109(4)

Results are given as means with s.e m. in parentheses

Resting anorectal angles were more obtuse in constipated patients than controls (p<0·01). Patients with intussusception had significantly more obtuse anorectal angles than those with no abnormality (p<0·01), or a rectocoele (p<0·05). There were no differences in anorectal angle between patients with rectocoeles, those with no abnormality and controls. Anorectal angles in patients with both abnormalities were similar to intussusception alone We hypothesize that, in constipation, a normal anorectal angle predisposes to rectocoele formation, whereas an obtuse angle predisposes to intussusception.

Cholinergic and serotonergic control of the internal anal sphincter in faecal incontinence

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Previous studies have shown that the α-adrenergic and intrinsic innervation of the internal anal sphincter is abnormal in idiopathic faecal incontinence (IFI). We have studied the effect of carbachol, a cholinoceptor agonist, and 5-hydroxytryptamine (5HT), a modulatory neurotransmitter acting directly on smooth muscle, on the internal anal sphincter.

Circumferential strips of internal anal sphincter from patients with IFI undergoing postanal repair and control patients undergoing abdomino-perineal resection for carcinoma were studied. Patients with IFI had preoperative anorectal physiology Responses to carbachol of seven controls (two female, five male) and six patients with IFI (all female) and responses to 5HT of eight controls (four female, four male) and seven patients with IFI (all female) were studied in organ baths The mean age (55 and 57 years) of the two groups was not significantly different

Carbachol produced relaxations in all strips The concentration–response curve to carbachol showed a significant insensitivity in incontinent patients at concentrations above 30 μM (p<0·05, unpaired t test). The maximum response was produced using 16·7 μM carbachol in controls and with 0·23 mM in patients with IFI (p<0·05) 5HT produced contractions in all strips The 5HT concentration–response curve was not significantly different in the two groups There was no difference in the concentration–response curves in male and female controls.

The decreased sensitivity to carbachol in idiopathic faecal incontinence suggests a dysfunction of cholingeric innervation which may be either extrinsic or intrinsic. The 5HT studies show that this component of the intrinsic neural regulation is intact and that the smooth muscle cells are capable of a normal contractile response

Improvement in viability of the gracilis neoanal sphincter after delayed transposition

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Initial attempts at the formation of an electrically stimulated gracilis neoanal sphincter were complicated by muscle necrosis and infection 5 of 11 cases. This may have been due to the segmental nature of the blood supply with inadequate perfusion of the distal part of the muscle[1] The vascular anatomy of the gracilis muscle was, therefore, studied by dissection, resin and radiocontrast injection in 13 postmortem and 7 cadaveric specimens.

There were 4, 3, 2 and 1 pedicles in 1, 16, 2 and 1 specimens, respectively, with a major contribution from the first perforating branch of the profunda femoris artery. Each artery entered the muscle on its posterolateral surface close to the anterior border to traverse it and give off ascending and descending branches These formed intramuscular arterio-arterial anastomoses with branches of the segmental artery above and to those below.

These potential direct intramuscular anastomoses have not been described previously. This knowledge has been applied by delaying the transposition of the muscle to the perineum for at least 14 days after dividing the distal pedicles. None of the 16 patients who have undergone this modified procedure has had muscle ischaemia or sepsis (cf conventional technique $p<0\cdot005$, Fisher's exact test)

1 Cormack GC, Lamberty BGH *The Arterial Anatomy of Skin Flaps* Churchill Livingstone, 1986, pp 353–5

Assessment of defective rectal evacuation by dynamic integrated proctography

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Dynamic integrated proctography (DIP) includes simultaneous measurement of puborectalis EMG activity and intrarectal pressure. This makes it uniquely suited in evaluating defects of rectal evacuation.

A total of 114 constipated patients underwent anal manometry, proctometrography and static anorectal angle measurement, in addition to DIP. Anismus was defined as recruitment of EMG activity of 50 per cent or more during straining. Of patients, 21 were poor evacuators (<40 per cent of contrast evacuated within 5 min), of which 9 were unable to evaucate any contrast. Parameters of the poor evacuators were compared to 50 patients who evacuated >90 per cent of contrast during proctography.

Poor evacuators had a reduced anorectal angle on straining [95(4) versus 110(3)*, $p<0\cdot01$]. There was a higher incidence of anismus (14 versus 12, ($p<0\cdot01$) and inability to achieve an intrarectal pressure of >50 mmHg on straining (8 versus 2, $p<0\cdot01$) in poor evacuators. Four patients who failed to evacuate demonstrated both EMG recruitment and failure to raise intrarectal pressure on straining, compared to 2 of the 62 who did evacuate ($p<0\cdot001$)

Anismus is a common cause of abnormal evacuation in constipated patients. A group exists in whom failure to raise intrarectal pressure is combined with EMG recruitment on straining. This represents a separate entity to anismus, not prevously described, which can only be defined by DIP

*S e m

Pulsed laser angioplasty; effect of arterial calcification

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We have performed 71 cases of laser-assisted angioplasty for occluded lower limb arteries using a pulsed-dye laser. Of these 71 cases, 19 have had evidence of marked discrete arterial calficiation on plain X-ray of the limbs, and the effect of plaque morphology on outcome was studied

	Calcified ($n=19$)	Non-calcified ($n=52$)	
Mean occlusion length (cm)	20±3·5*	21·6±2·0*	$p=$n s †
Technical success	53%	85%	$p<0\cdot01$
Clinical success	47%	69%	$p<0\cdot1$ (n s)

* ±s e m., † χ^2 test

The commonest cause of failure was arterial dissection, which occurred immediately proximal to the calcified area in all cases

A bench model of calcified disease was developed and suggested that the increased rigidity of calcific plaque combined with pressure from the delivery device applies torque to the artery leading to eccentric tracking of the laser catheter. This phenomenon has also been observed intra-operatively using duplex scanning. In technically successful cases cumulative patency was 53 per cent in calcified and 62 per cent in non-calcified arteries at 7 months ($p=$n s , log rank test)

The adverse effect of calcification on outcome is due to the morphology and not the length of the occlusion. Although significantly fewer cases were recanalized in the calcified group, subsequent patency in technically successful cases is equivalent to that seen in non-calcified cases. Improvement in outcome in calcific disease will probably come from advances in delivery device control

Estimation of the incidence of anismus by laboratory tests

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Anismus is considered to cause obstructed defaecation. The diagnosis is usually made by laboratory-based EMG studies or videoproctography. These are unphysiological investigations. We have investigated 11 female patients with obstructed defaecation [age 34 years (17–34)*] and used computerized ambulatory anorectal EMG and pressure monitoring in the patients' home environment to determine conditions. Laboratory resting pressures (LRP) and average ambulatory pressures (AAP) were similar [LRP 89 cmH_2O (48–117) versus AAP 90 (60–120)], as were the anorectal pressure gradients [laboratory +84 (+42 to +113) versus ambulatory +76 (+18 to +100)]. Straining to evacuate in the laboratory raised anal pressures [123 (50–173) versus LRP, $p<0\cdot01$] but the high anorectal pressure gradient remained [+92 (−80 to +119); n s]. This was accompanied by EMG evidence of puborectalis recruitment [EMG activity +200 per cent (+50 to +912 per cent)]. In the home environment, anal pressures during evacuation dropped significantly [28 (0–113) versus AAP, $p<0\cdot01$] and the anorectal pressure gradient was more significantly in favour of successful evacuation [+5 (−167 to +67), $p<0\cdot01$]. Puborectalis EMG activity showed significant inhibition [−25 per cent (−400 to +1100 per cent); $p<0\cdot05$ versus laboratory measurements]. Only 2 of the 11 patients with laboratory anismus had EMG evidence of this diagnosis in more normal physiological surroundings

Our findings question the significance of anismus as currently diagnosed

* Median(range)

Metal versus sapphire tip laser recanalization: comparison of arterial injury and ablation efficiency

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Use of continuous wave Nd-YAG laser for peripheral laser angioplasty remains attractive because of its multidisciplinary role in medicine. Thermal injury is, however, a potential problem with currently available delivery devices. The aim of this study was to measure and compare the vaporization efficiency and extent of associated arterial injury produced by metal-tipped and transparent sapphire-tipped delivery catheters.

An *in vitro* model was used to produce 40 laser channels in aortic sections immersed in blood using 10 J and 20 J energy with each device. Serial histological sections of each channel were stained to identify denatured wall collagen and analysed by digital image processing. Two measurements were made, depth of the channel and injury i.e. the extent of collagen denaturation lateral to the margins of the lased channel

	Energy (J)	Sapphire	Metal	p value
Depth	10	990(140)	710(170)	<0·05
(μm)	20	1333(190)	1010(200)	<0·05
Injury	10	350 (60)	810(180)	<0·001
(μm)	20	390(100)	750(320)	<0·05

Statistical analysis was by one-way ANOVA. Results are given as means(s d.)

In addition, intimal tearing and coagulum formation were more evident with the metal device

These experiments suggest that if a continuous wave Nd-YAG laser is used, sapphire tip delivery may be safer than metal tips by producing more efficient forward vaporization and minimal thermal injury to the surrounding arterial wall

Role of β-carotene in pulsed laser angioplasty

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Preferential absorption of light by atheroma is largely due to its increased carotenoid content compared to normal arterial wall. Five atherosclerotic male New Zealand white rabbits were given 1 ml kg^{-1} β-carotene i.v. twice weekly. Rabbits were killed at 1, 6 and 24 h, or 7 or 29 days following the first injection. One further rabbit acted as a control. Samples of serum, fat, muscle, urine, bile and artery were analysed for β-carotene content.

	β-Carotene levels in tissue				
Time	Serum (μg ml^{-1})	Plaque (μg g^{-1})	Normal artery (μg ml^{-1})	Urine (μg ml^{-1})	Bile (μg ml^{-1})
Control	0	0	0	0	0
1 h	987	13	5·1	0	0·04
6 h	826	88	2·7	0	2·1
24 h	81	56	3·3	0	0·5
1 week	3	157	6·4	0	0·03
29 days	14	118	0·7	0·21	0·30

Penetration of β-carotene into atheromatous plaque occurred from the endothelial surface, reaching the full thickness of the plaque at one week.

Ablation thresholds for normal and atheromatous arterial wall were measured using a pulsed dye laser at 480 nm. In the control, the ablation threshold for normal arterial wall was 30 mJ, compared to 20 mJ for atheroma (3·2). In all the β-carotene injected rabbits, the thresholds for ablation of normal artery fell to 17·5 mJ, whilst in atheroma it fell to 5·8 mJ ($p<0{\cdot}05$, two-sample t test), widening the differential to 3:1.

β-Carotene is taken up preferentially by atherosclerotic plaque. This is associated with an increase in the differential ablation threshold for plaque compared to normal arterial wall. The administration of β-carotene may enhance the efficacy of human laser angioplasty.

Photoplethysmographic peripheral pulse waveform characteristics in screening for peripheral vascular disease

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Photoelectric plethysmograph (PPG) pulse wave signals were recorded from the toes of patients attending the vascular laboratory for exercise testing with Doppler pressure index measurements. Time from the ECG-Q wave to various reference points on the pulse waveform curve were measured for both legs in 28 patients with exercise-induced pain most severe in one leg and in 17 matched controls. The results were compared to the Doppler findings to assess the value of PPG as a screening test for peripheral vascular disease.

All controls had normal Doppler indices, whereas 27 of the 28 patients had low values of $<0{\cdot}90$ or a fall after exercise of $>0{\cdot}20$ (6 abnormal only after exercise). For PPG, timing measurements to the peak of the pulse waveform most consistently showed the largest difference (>30 ms) between the legs of patients. All controls had normal peak-PPG measurements. Peak-PPG timing was abnormal in 25 (one abnormal only after exercise) of the 27 patients with abnormal Doppler indices (sensitivity 93 per cent). The one patient with normal Doppler indices had an abnormal peak-PPG and angiography confirmed iliac and tibial artery disease, suggesting that PPG was more sensitive than Doppler examination in this patient.

The results suggest that peak-PPG times can reliably identify patients with peripheral vascular disease.

Prediction of irreversible lower limb ischaemia using ^{31}P magnetic resonance spectroscopy in the resting foot

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Following revascularization of a critically ischaemic limb, further clinical deterioration may occur due to irreversible muscle ischaemia. This study uses ^{31}P magnetic resonance spectroscopy to detect the presence of irreversible muscle ischaemia in the small muscles of the resting foot.

Twenty-one subjects with critical ischaemia and 10 controls without any evidence of peripheral vascular disease were studied. Spectra were obtained using a 1·6 T whole body cryomagnet with a solenoidal coil. The phosphocreatine (Pcr) to inorganic phosphate (P_i) ratio and the intracellular pH were obtained from the spectra of the foot in the plane containing the maximum muscle bulk.

The patients were divided into two groups. Group 1 consisted of nine patients who underwent a reconstruction and had a viable limb at one month, or who were deemed not to require surgical intervention. Group 2 consisted of 12 patients who had a surgical reconstruction that failed within one month, or who were scanned just prior to amputation.

	Control ($n=10$)	Group 1 ($n=9$)	Group 2 ($n=12$)
Pcr/P_i	4·5	3·5	2·4 ($p=0{\cdot}0001$)
pH	7·12	7·12	7·12

The Pcr/P_i ratio as a measure of oxidative phosphyloration is significantly lower in group 2 with irreversible muscle ischaemia at rest.

Comparison of three methods of measuring cigarette smoking in patients with peripheral vascular disease

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Although smoking has been identified as an independent risk factor in peripheral vascular disease and postoperative graft failure, smokers do not accurately report their habit. Therefore, a cheap, non-invasive objective method of measuring smoking behaviour in vascular surgical units would be desirable. We have compared the value of end expiratory carbon monoxide monitoring (Bedfont Technical Instruments) which is both simple and inexpensive, with two well established validated techniques (serum thiocyanate and carboxyhaemoglobin, CoHb, levels). Thirty three surgical patients with peripheral vascular disease provided samples of expired air for CO measurement and blood for CoHb and thiocyanate levels. Nineteen patients claimed to be non-smokers (2 inaccurately) and 14 were smokers. The most sensitive measure was CoHb (see table), which also had a high specificity. CO was comparable to CoHb in terms of its specificity but was not as sensitive. The CO and CoHb levels were shown to correlate significantly ($r=0{\cdot}829$, $p=0{\cdot}0001$, Spearman rank correlation). Thiocyanate was not as sensitive or specific as had been anticipated.

	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
CoHb	90	100	100	95
Thiocyanate	80	70	82	76
CO	60	100	100	73

Conventional methods of assessing smoking behaviour have not gained widespread use because they are time-consuming, relatively invasive and require technical support. Non-invasive CO measurement gives immediate accurate results and is a useful, inexpensive method of measuring smoking behaviour in patients attending a follow-up vascular unit.

Dipyridamole-thallium myocardial imaging before aortic reconstructive surgery

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Myocardial infarction accounts for over one-half of the early and late mortality of aortic surgery and dipyridamole-thallium imaging has been proposed as the ideal screening test to determine cardiac risk[1]. This study investigates the results of such a screening policy.

Over 30 months, 65 patients were prospectively studied. 36 had positive scans; 29 had negative scans. The age and sex distributions of the two groups were not significantly different. Two patients died, both had negative scans. Ten patients with positive scans suffered cardiac complications, compared with two in the other group ($p<0{\cdot}05$). Six patients with positive scans suffered myocardial infarction compared with none in the other group ($p<0.05$)

There were no significant differences in the length of time in intensive care, hospital stay or the mortality between the two groups All ten patients who suffered cardiac complications (including myocardial infarction) had clinical and/or electrocardiographic evidence of preexisting cardiac disease

The value of a policy of routine dipyridamole-thallium myocardial imaging before aortic reconstructive surgery is questionable

1. Boucher CA, Brewster DC, Clement Darling R *et al* Determination of cardiac risk by dipyridamole-thallium imaging before peripheral vascular surgery. *N Engl J Med* 1985, **312** 389–95

Effect of claudication on systemic capillary endothelial swelling

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Reperfusion injury following severe ischaemia results in endothelial damage, increased permeability and hence cell swelling. Recent work has demonstrated systemic vascular injury after lower limb ischaemia and suggested that this may occur after the transient ischaemia of intermittent claudication. An animal model has been developed to further investigate this phenomenon

Male Sprague-Dawley rats were subjected to 14 days of intermittent, pulsed electrical stimulation to the right hindlimb (10 Hz, 10–15 min, seven times daily), following common iliac artery ligation and the implantation of electrodes adjacent to the lateral popliteal nerve This regimen induced repeated muscle contraction in an ischaemic limb and produced circulatory and morphological changes similar to those seen in human claudicants, but not muscle necrosis

Electron microscopy revealed a significantly increased number of swollen capillary endothelial cells in muscle biopsies from the 'claudicating' limb compared to controls which had sham operation ($p<0.001$), stimulation only ($p<0.001$) or artery ligation alone ($p<0.05$) Similar, significant changes were also seen in the left hind limb and also in the spinotrapezius, diaphragm and left ventricular muscles

These results indicate that intermittent stimulation of partially ischaemic muscle is associated with systemic endothelial damage and provide further evidence suggesting that intermittent claudication incites systemic vascular injury

Effect of polyunsaturated fatty acids on doxorubicin sensitivity in MCF-7 cells

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Polyunsaturated fatty acids (PUFA) are capable of altering the growth of breast cancer cells *in vitro* We investigated the effect of pretreatment with the PUFA linolenic acid (GLA) on doxorubicin sensitivity in MCF-7 cells.

MCF-7 cells were cultured with GLA (20 or 30 μg ml^{-1}) for 24 h and then exposed to 0·1, 0·4 or 0·8 μm doxorubicin for 1, 2 or 18 h Cell viability was measured by MTT assay (tetrazolium) 4 days later

Doxorubicin exhibited a cytotoxic effect in a dose-dependent and time-dependent fashion GLA alone (20 μg ml^{-1}) had no effect on cell growth but at 30 μg ml^{-1} caused growth inhibition greater than 0 1 μm doxorubicin (54 9 versus 75 per cent, $p<0.05$), but similar to that of 0 4 and 0 8 μm doxorubicin ($p=0.49$)

	Growth inhibition (%)		
		GLA pretreatment (μg ml^{-1})	
Doxorubicin (μm)	Control	20	30
0·1	54 9	74 0 ($p<0.05$)	84 9 ($p<0.001$)
0·4	70·0	79 9 ($p<0.05$)	91·8 ($p<0.001$)
0 8	70 9	82 9 ($p<0.005$)	91·1 ($p<0.001$)

These data demonstrate that GLA at lethal and sub-lethal doses can enhance doxorubicin sensitivity of MCF-7 cells *in vitro*

Role of cyclical sequential hormonochemotherapy in advanced breast cancer

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Evidence from studies *in vitro*[1] suggests that pretreatment with hormones may increase the efficacy of cytotoxic drugs in breast cancer

We now present survival data on 51 patients treated with priming doses of hormones followed by cyclical chemotherapy. The regimen comprised ethinyloestradiol for 1 week, medroxyprogesterone acetate for 2 weeks, followed by alternating cycles of doxorubicin + vincristine and cyclophosphomide + methotrexate + 5-fluorouracil every 3 weeks. to a complete course of three double cycles Of patients, 43 completed the course. Of these, 17 (40 per cent) achieved a complete response according to U I.C C criteria, with a relapse-free survival of 22 months Nineteen patients (44 per cent) showed partial response with a relapse-free survival of 10·6 months and seven patients (16 per cent) failed to respond. Eight patients died before completing the course of treatment The relapse-free survival was significantly longer for complete responders than for partial responders ($p<0.05$) Subjective responses, assessed by Karnofsky's performance status, showed significant improvement post-treatment The most frequent toxicity with chemotherapy was hair loss, and mild nausea and vomiting No side effects were observed with hormone therapy We have shown an overall response rate (complete + partial) of 84 per cent with this treatment compared to other trials using endocrine or chemotherapy alone.

Encouraged by the above results, we have now embarked on a double-blind clinical trial comparing hormonochemotherapy and chemotherapy alone.

1 Botenbal M, Sonnenveld P, Foekens JA and Klijn JGM. Oestroadiol enhances doxorubicin uptake and cytotoxicity in human breast cancer cells (MCF-7) *Eur J Cancer Clin Oncol* 1988; **24** 1409–14

Effect of high loading-dose tamoxifen on early prediction of response to anti-oestrogens in locally advanced breast cancer

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Tamoxifen is widely used as an effective treatment for locally advanced breast cancer in the postmenopausal woman, particularly in the elderly. A method which predicts which patients would respond to anti-oestrogen would enable the non-responders to be offered alternative treatment, such as surgery, earlier than the several months it takes for conventional therapy. A high dose loading regime was therefore planned to see if response could be obtained earlier

Forty-three postmenopausal patients with locally advanced breast carcinoma were treated with 100 mg tamoxifen daily for 2 weeks and thereafter 40 mg daily as their primary treatment Tumour size in two directions was serially measured Side-effects were minimal, with nausea and tiredness recorded, and did not interfere with 100 per cent compliance.

After the 2 week loading dose, 10 patients (23 per cent) showed good response (>50 per cent decrease in tumour size) and 19 patients (44 per cent) moderate response (25–50 per cent decrease in tumour size), totalling 67 per cent of patients All but one of these patients maintained their response at follow-up up to 2 years Eight out of 13 patients who failed to show a response at 2 weeks continued to fail to respond long-term

A high dose loading regime of tamoxifen for 2 weeks successfully predicts a group of postmenopausal patients with locally advanced breast cancer who will respond to anti-oestrogens As a method it is less efficient at identifying all the non-responders and further investigations are planned in this study

Use of the tumour marker, CA15-3, in detection of bone metastases in breast cancer patients

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Early detection of bone metastases in patients with breast carcinoma can limit the morbidity from the adverse sequelae of osteolysis Serial isotope bone scanning, though most sensitive, has financial and labour drawbacks. We studied the value of the tumour marker, CA15-3, as an alternative to bone scintigraphy.

A total of 218 patients with breast carcinoma were studied over a 4-year period. Venous CA15-3 assays were obtained at 3-monthly intervals and bone scintigraphy annually.

In 33 patients with metastatic disease, elevated CA15-3 levels recorded at the time of diagnosis of metastases were as follows: bone metastases = 15/17 (88 per cent); non-bone metastases = 2/6 (33 per cent); both bone and non-bone metastases = 7/10 (70 per cent). This preponderance of an elevated CA15-3 in metastatic bone disease resulted in a sensitivity, specificity and positive predictive value of 81·5, 66 and 92 per cent, respectively. Although 22/27 patients with bony secondaries showed an elevation of the tumour marker at the time of diagnoses of the metastases, the remaining five patients subsequently showed a similar, albeit delayed, increase. Thus all of our patients with bony metastases had a raised CA15-3 level.

In conclusion, we recommend CA15-3 as a simple, reliable and inexpensive method of detecting bone metastases in patients with breast cancer.

Treatment of the axilla in operable breast cancer

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Many surgeons use axillary node sampling and radiotherapy in node-positive breast cancer as definitive treatment of the axilla. We have examined the value of this policy.

A total of 1681 women were treated surgically for breast cancer between 1976 and 1988 and have been followed up for at least 12 months.

	Wide local excision	Simple mastectomy	Patey mastectomy
Number treated	450	687	544
Axillary recurrence	82 (18%)	157 (23%)	28 (5%)
Recurrence controlled by			
Axillary clearance ±DXT	14/16	12/13	–
Excision of tumour ±DXT	16/31	38/68	7/11
Radiotherapy alone	1/3	9/22	2/4
Systemic therapies alone	8/32	15/44	1/11
Recurrence uncontrollable	43/82	83/157	18/28

Axillary clearance is the treatment of choice for axillary recurrence after surgical treatment of breast cancer. But if performed at the time of initial surgery, it would prevent recurrence in all but the most aggressive cases.

p53 abnormalities in human breast cancer

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p53, a nuclear phosphoprotein important in cell division, is a key factor in human malignancy. Loss of normal p53 tumour suppressor function and/or overexpression of mutant, oncogenic p53 are important steps in carcinogenesis. The aim of this work was to define p53 abnormalities in breast cancer.

From 65 snap-frozen tumours, deoxyribonucleic acid (DNA) and ribonucleic acid (RNA) were extracted. Southern blots of paired blood/tumour DNA were probed for allele losses around the p53 locus. Using the polymerase chain reaction, p53 DNA was selectively amplified and sequenced to detect mutations. p53 gene messenger RNA expression was determined from Northern blots and p53 protein detected by immunocytochemistry on frozen sections.

p53 allele losses were detected on 19/45 (42 per cent) of tumours and gene mutations identified in 13. p53 messenger RNA expression (detected in 38/65, 58 per cent of tumours) and immunocytochemically detected protein (in 13/44 examined, 29 per cent) did not correlate with p53 DNA changes.

This study presents the first comprehensive analysis of p53 in breast cancer. It demonstrates that loss of one p53 tumour suppressor gene and mutation of the remaining p53 to an oncogene occur in the same tumour, but indicates that the regulation of p53 expression in breast cancer is complex.

Reliability of flow cytometric measurements of cell kinetics

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Analysis of tumour DNA by flow cytometry is widely used. It is suggested that cell kinetic measurements can be made by calculating the proportion of cells in S phase (SPF). As we are sceptical of these claims we have determined the variability of SPF, and its correlation with direct measures of DNA synthesis.

Three cohorts of tumours were studied. From 121 primary breast cancers, 112 (93 per cent) DNA histograms were obtained, with 100 (89 per cent) interpretable for SPF. Two observers calculated SPF on two occasions. The rank correlation coefficients were: observer A, 0·960; observer B, 0·962; and inter-observer correlation 0·928. However, using the method of Bland[1], the mean difference between the observer estimates was 14 per cent (confidence limits 8–20 per cent), and the normal range for estimates was ±40 per cent.

In a separate group of 61 tumours, SPF and *in vitro* thymidine labelling index were calculated and the correlation coefficient of these was 0·117. A further 41 tumours were labelled *in vivo* with bromodeoxyuridine, and the labelling index and SPF determined, with a correlation coefficient of 0·681.

Despite high apparent inter-observer and intra-observer correlation, more subtle analysis shows that the SPF is not a reproducible measurement and does not correlate well with thymidine or bromodeoxyuridine labelling indices. Its potential as an indicator of tumour behaviour is therefore questioned.

1. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet* 1986; i: 307–10.

Bromodeoxyuridine-derived *in vivo* proliferation indices of invasive breast carcinoma: a study of 60 tumours

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Cell proliferation may contribute to the aggressiveness of breast cancer. Past measures of proliferation such as the S-phase fraction are not entirely satisfactory. *In vivo* labelling of human breast tumours with bromodeoxyuridine is safe and reproducible. Multiparameter flow cytometry allows measurement of the DNA index, labelling indices (LI), S-phase duration (T_s) and the potential doubling time (T_{pot}) of the pulse-labelled tumour.

Sixty patients with proven invasive breast carcinoma consented to receive an intravenous bolus of 250 mg bromodeoxyuridine between 2 and 8·6 h prior to mastectomy. Biopsy specimens were preserved in 70 per cent ethanol and disaggregated in pepsin. Of tumours, 55/60 yielded a measurable LI, and T_s and T_{pot} data could be calculated in 38 tumours. Intratumour variation was studied in 17 tumours using multiple biopsies. There were no significant differences in the total LI, T_s or T_{pot} between node-negative and node-positive tumours (*Table*).

Index	*n*	Mean	Range	Median
Note-negative tumours				
Total LI (%)	21	4·9	1·2–12·3	4·2
T_{pot} (days)	15	9·2	1·8–40·6	5·7
Node-positive tumours				
Total LI (%)	34	4·7	0·7–15·0	4·1
T_{pot} (days)	23	10·4	3·0–30·1	8·6

In vivo static and dynamic proliferation indices appear to be an incomplete measure of the biological aggressiveness of invasive breast carcinomas as reflected in their lymph node status.

Nodo-nodal anastomosis for treatment of lymphatic obstruction

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Lymph node to vein anastomosis or lymphatic vessel to vein anastomosis have been unsuccessful in the treatment of primary lymphoedema. The enteromesenteric bridge operation has been shown to form connections between bowel and distal lymphatics but its use is limited for cases with a localized proximal obstruction and healthy distal lymphatics[1]. We have tested a new technique of nodo-nodal anastomosis in 11 rabbits. The popliteal lymph node was dissected free from all tissues including its blood supply, preserving its afferent and efferent lymphatic vessels. The lymph node was divided in half then resutured with the help of a microscope. Twelve anastomoses were performed in 11 rabbits. Lymphangiography with lipidol was undertaken 7 days later in all limbs. In three of these rabbits, a lymph node autotransplantation was also performed, interposing between the two halves another divided node. Additional lymphangiography was performed after 1 and 2 months.

All but one of the anastomoses were patent at the time of lymphangiography, the exception was one animal where the efferent lymphatic vessel could not be seen. The patency rate was 92 per cent. This method is much easier to use that microlymphatic vessel to vessel anastomosis[2] and may be of clinical value.

1. Hurst PAE, Stewart G, Kinmonth JB, Browse NL. Long term results of the enteromesenteric bridge operation in treatment of primary lymphoedema. *Br J Surg* 1985, **72**: 272–4
2. Ho LC, Lai MF, Yeats M, Fernandez V. Microlymphatic bypass in obstructive lymphoedema. *Br J Plastic Surg* 1988, **41**: 475–85

Short-term venous hypertension and the microcirculation

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The purpose of this study was to examine the effects on the skin microcirculation of a short period of venous hypertension. Thirty-four subjects (17 patients with lipodermatosclerosis and 17 controls) were studied. Laser-Doppler flowmetry was used to assess the hyperaemic responsiveness of the skin following 3 min ischaemia. Thirty min venous hypertension (VH) was applied, the hyperaemic responses were then repeated.

In controls, the median hyperaemic response as expressed as a ratio of peak to basal flow was 2·25 (interquartile range, IQR 1·6–3·1) before VH, after VH, this fell to 1·7 (IQR 1·2–2·4, $p<0{\cdot}04$). The time taken to reach peak flow was 10 s (IQR 9–16·5) before VH, rising to 20 s (IQR 11·5–26) after VH ($p<0{\cdot}01$). The peak base ratio in liposclerotic skin before VH was 1·0 (IQR 0·8–1·6), i.e. no hyperaemic increase in flow was observed. After VH, the median ratio was 1·05 (IQR 0·7–1·5), an insignificant difference. Time taken to reach peak flow rose from 21 s (IQR 18·5–24) before VH to 24 s (IQR 20–67·5) after VH, a small but statistically significant increase ($p<0{\cdot}05$).

The results suggest that a short period of venous hypertension causes an immediate deficit in microcirculatory function, which may indicate the nature of the pathophysiological mechanisms underlying skin damage in venous disease.

Deep vein valve construction *in situ*: static, dynamic and long term properties

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A technique of *in situ* autogenous deep vein valve construction has been developed for correction of deep vein reflux in the calf pump failure syndrome. Forty one valves were constructed in the canine femoral vein. All were patent at ascending phlebography and 38 were competent at descending phlebography.

Hydrostatic testing was performed on 27 valves and 24 were competent at pressure gradients of 0·2–250 cmH$_2$O. Hydrodynamic testing was performed on nine valves at a contractiong rate of 40 cycles min^{-1} and at varying stroke volumes. Results (mean ±s.e.m.) are shown in the *Table*.

Stroke volume (ml)	Flow rate (l min^{-1})	Pressure gradient (cmH$_2$O)	Regurgitation fraction (%)
16·80±0·21	3·29±0·08	56·44±16·47	8·19±0·87
26·49±0·16	5·07±0·07	52·04±11·39	6·84±0·83
34·12±1·00	6·48±0·22	16·44± 5·39	3·28±1·13

Twelve valves were studied 112 days after construction. All were patent with no luminal thrombosis. Four were competent at descending phlebography. Light and scanning electron microscopy revealed healthy endothelium, but cusp adherence to the vein wall in incompetent valves, possibly caused by low valve pressure gradients in the animal model.

In situ valve construction produces a valve with favourable static and dynamic properties that is resistant to thrombosis and may be suitable for correction of deep vein reflux in man.

Investigation of vein graft spasm

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Vascular spasm is well recognized, although the mechanisms involved are poorly understood. Recently, the vascular endothelium has been recognized as having the potential to alter vessel tone by its production of the endothelium-derived relaxing factor (EDRF). When a vein is grafted into the arterial circulation, the endothelium is damaged. Although a neoendothelium develops, little is known about the effect these cells may have on vein graft (VG) vasoreactivity. This study was designed to examine human VG endothelial function. The study compares the vasomotor function of human saphenous vein (SV) with the function of failed SV previously grafted into the coronary circulation, obtained at the time of redo coronary artery bypass surgery. Production of EDRF was examined as a sensitive indicator of endothelial function. Rings of SV ($n=13$) and VG ($n=11$) were suspended under isometric tension in an organ bath and precontracted with noradrenalin (10 μM) and then exposed to acetylcholine (ACh, 10 nM–10 μM), a receptor-mediated stimulus of EDRF production. ACh induced a significant relaxation (21·7±3·1 per cent, $p=0{\cdot}02$) in the SV. In marked contrast, ACh did not relax the VG. The importance of the impaired endothelial function was examined in response to histamine, an agonist known to stimulate production of EDRF. The sensitivity to histamine in the VG was significantly increased compared to SV (median effective dose 3·2±0·9 versus 30·0±13·2 μM).

These results show that the VG neoendothelium has impaired function and that this is associated with VG supersensitivity to histamine. Vein graft spasm is documented in the literature[1] and this study provides a possible mechanism for this phenomenon.

1. Takatsu F, Ishikawa H, Nagaya T. A case with spasm of a saphenous vein graft. *Jpn Heart J* 1987, **28**: 947–53

Prostacyclin production by seeded vascular grafts

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Endothelial cell seeding has been proposed as a method to improve the patency rates in small calibre prosthetic vascular grafts. *In vivo*, endothelial cells normally produce prostacyclin (PGI$_2$), a potent anti-platelet agent. The aim of this study was to determine whether seeded grafts show significant PGI$_2$ production after *in vivo* implantation.

Five dogs had bilateral polytetrafluoroethylene (PTFE) grafts (4 mm internal diameter) implanted in their femoral arteries. On one side the graft was seeded with a confluent layer of autologous endothelial cells, whilst the contralateral side was plain PTFE. Twelve weeks after implantation the grafts were removed. At this time, all five control grafts had occluded, but only one of the seeded grafts had done so ($p=0{\cdot}025$). Two 5-mm circular punch biopsies were taken from the central portion of each graft and also from the corresponding dog's abdominal aorta. Basal and thrombin-stimulated PGI$_2$ release were then assessed (via 6-keto-PGF$_{1\alpha}$) from each biopsy. Results are given as means±s.d.

	Prostacyclin release (pg min^{-1})		
	Aorta	Seeded	Control
Basal	125±56	25·3±10·8†,*	3·0±3·8**
Stimulated	530±11	303±110‡,*	11·4±8·8**

*$p<0{\cdot}05$; **$p<0{\cdot}01$ versus aorta
†$p<0{\cdot}05$, ‡$p<0{\cdot}01$ versus control

In conclusion, this study has shown that endothelial cell seeding does result in a functional graft lining producing PGI_2, but this is not equivalent in magnitude to native artery This dynamic release of PGI_2 explains one of the reasons for the significantly superior early graft patency seen with seeded grafts.

Influence of antiplatelet therapy on graft maturation

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Thromboxane synthetase inhibitors may be ideal anti-platelet drugs and may be indicated to preserve patency in vascular grafts The effect of thromboxane synthetase inhibition on the healing of knitted dacron was investigated in a canine model and compared with cyclooxygenase inhibition and placebo.

Greyhounds ($n=30$) were randomized to aspirin (150 mg) and dipyridamole (50 mg) (ASA+DPM), a thromboxane synthetase inhibitor (CGS12970; CIBA-Geigy) or placebo twice daily for 48 h prior to implanting 6-cm lengths of 6 mm dacron (Meadox Microvel) in the femoral artery At two months the grafts were removed, opened, photographed and the percentage thrombus-free area of the lumen measured by planimetry Longitudinal sections of the proximal and distal anastomoses stained by haematoxylin and eosin were examined blind by a pathologist and a surgeon for perianastomotic neointimal thickness, pannus and endothelial cell ingrowth (μm) Transverse sections at the midgraft were measured for percentage luminal occlusion

The percentage thrombus-free area was increased from 15·1±2·2 in placebo to 35·3±5·0 with ASA+DPM ($p<0{\cdot}01$) and to 46·6±5·2 with CGS12970 ($p<0{\cdot}0001$). Midgraft occlusion was significantly reduced by CGS12970 from 48·2±5·9 per cent in placebo to 33·9±2·7 per cent ($p<0{\cdot}05$) but not by ASA+DPM at 44·2±8·6 per cent. Only CGS12970 had a significant effect on graft maturation: reducing proximal and distal neointimal thickness ($p<0{\cdot}05$) and increasing pannus and overlying endothelial cell ingrowth ($p<0{\cdot}05$) (Mann–Whitney)

Thromboxane synthetase inhibition could preserve vascular graft patency by reducing luminal thrombus deposition and anastomotic neointimal hyperplasia and by promoting endothelialization

Viability of distal arterial reconstruction

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Surgeons are increasingly required to justify therapeutic regimes on economic grounds We have studied 120 arterial reconstructions to crural vessels in the lower third of the calf, performed for critical ischaemia Results were assessed against a primary amputation rate of 3 per cent, at mean follow-up 35 months (range 5–75 months).

The primary procedure remains successful in 43 per cent of cases, in a further 24 per cent, success was dependent on additional operations (mean 2·3 per patient). In 33 per cent, the procedure culminated in amputation despite reoperation (mean 2·6 operations per patient, i e leg salvaged in 67 per cent at 3 years).

Average costs to the hospital were similar. £9683 for amputation and £9750 for reconstruction and its sequelae Mobility rates differed significantly· 38 per cent amputees were wheelchair or bed bound whilst all successful reconstructions were independently mobile. Mobility outside the home was achieved in 79 per cent of reconstructions but only 31 per cent of amputees.

In conjunction with health economists we have calculated the minimum 3 year graft patency rates necessary to achieve cost equivalence between femorocrural reconstruction and amputation. A primary graft patency of 43 per cent at 3 years reaches equivalence. When primary patency is 36 per cent, a secondary patency of 20 per cent is necessary.

We consider that these figures can be used in conjunction with local vascular audit to justify an active approach to the management of critical ischaemia

Rehabilitation of vascular amputees

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In the UK, 5000 lower limb amputations for vascular disease occur annually. This study assesses the results the number referred for prosthetic fitting and the eventual rehabilitation and wheelchair dependence.

All lower limb amputations performed in 1986 and 1988 in eight hospitals in the south-east region were assessed. Of 440 vascular amputees, 193 were above knee (AK), 193 below knee (BK), 15 Gritti-Stokes (GS), 15 through knee (TK) and 24 bilateral Of these, 252 (57 per cent) were referred for prostheses. Rehabilitation questionnaires were sent to 179 (41 per cent), as 54 had died and 19 had become non-wearers prior to commencing the study The response rate was 81 per cent.

Of patients, 102 completed the questionnaire, 31 BK, 56 AK, 11 bilateral, 3 GS and 1 TK amputation. A total of 21 patients had died and 22 had become non-wearers Out of a maximum rehabilitation score of 12, 52 patients scored 6 or more, consistent with mobility on their artificial limb around the home. A further 21 scored 9 or more: a standard accepted as successful rehabilitation Sixty-one patients used a wheelchair less than half their waking hours and 22 never used one

We conclude that 10–15 per cent of vascular amputees will achieve mobility around the home on their prosthesis Only 5 per cent, however, rehabilitate well and become independent of their wheelchair

Role of polyamine biosynthesis in gastric mucosal cytoprotection and ulcer healing in the rat

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Healing of gastric mucosal ulceration is enhanced by acid-reducing drugs but the mucosal proliferative response to injury is also important and is moderated by many factors including luminal availability of epidermal growth factor (EGF) and hormones including gastrin. 2,3-Difluoromethyl ornithine (DFMO) is a specific inhibitor of ornithine decarboxylase, the rate-limiting enzyme in polyamine synthesis necessary for DNA replication

The citric acid to serosa model of gastric ulceration was used in 40 rats After 1 week pretreatment, the untreated group had a mean ulcer area of 0·253±0·035 cm^2. This was not affected by pretreatment for one week with omeprazole (400 μmol ml^{-1} kg^{-1} day^{-1}) giving an area of 0·293±0·024 cm^2 (n.s.) One week pretreatment with 2 per cent DFMO in drinking water increased ulcer area to 0·455±0·04 cm^2 ($p<0{\cdot}01$) Subsequently achlorhydric rats (omeprazole) showed 60 per cent healing leaving an area of 0·116±0·01 cm^2, which exceeded that of controls ($p<0{\cdot}01$). Healing in omeprazole+DFMO cotreated rats was inhibited by 52 per cent (0·32±0·025 cm^2, $p<0{\cdot}05$)

We concluded that polyamine biosynthesis is necessary for mucosal cytoprotection and ulcer healing independent of achlorhydria and may be a common second messenger for proliferative modulations.

New oesophageal sphincter function index

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The competence of the cardia depends on lower oesophageal sphincter pressure (LOSP), the length of the sphincter in the abdomen and the overall length of the sphincter. We have devised an index (SFI) which gives better discrimination between patient groups than any one of the above factors taken separately. SFI is calculated as the product of sphincter pressure and the percentage of the sphincter length (PL) exposed to abdominal pressure Eighty patients had routine endoscopy, manometry and 24 h pH studies, and were entered into the following diagnostic groups, normal ($n=21$), nutcracker ($n=12$), reflux ($n=21$) and Barrett's ($n=26$). Results are given in the *Table* as means ±s.e.m.

	Normal	Nutcracker	Reflux	Barrett's
SFI	973±107	1326±108**	393±51**	180±25**
LOSP (mmHg)	14·2±1·3	18·6±1·4*	11·1±1·3	6·1±0·7**
PL (%)	(67±2·4 n.s. 71·2)**		(37±3·5 n.s. 32·7±3)	

*$p<0.001$, **$p<0.01$

The SFI values discriminated between all four groups. There was a statistically significant difference between the Barrett's group and the normal group, but not between the reflux and the normal groups for LOSP. The PL values were significantly different for the normal and nutcracker groups compared to the reflux or Barrett's groups, but did not discriminate between the reflux and Barrett's group. When the Barrett's and reflux groups were combined, there was a significant difference for the SFI versus the normal group.

The calculation of the sphincter function index, SFI, gives better discrimination than LOSP or PL alone and may be useful in evaluating response to treatment.

Prospective randomized trial of Nissen fundoplication and Angelchik prosthesis in the surgical management of medically refractory gastro-oesophageal reflux

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There is controversy regarding the best surgical procedure for gastro-oesophageal reflux that is refractory to medical therapy. We have thus carried out a prospective randomized trial of Nissen fundoplication and Angelchik prosthesis in a specialist unit, with all procedures performed by one surgeon.

Over a 3-year period, 50 patients were randomized to undergo either a floppy Nissen fundoplication ($n=25$) or Angelchik prosthesis insertion ($n=25$). The groups were matched for age, sex, duration of symptoms and medical therapy. All patients underwent pre-operative upper gastrointestinal endoscopy, barium studies, manometry and 24-h pH testing.

There was no operative mortality. The operating time was (median, range) 50 (35–95) min with Nissen and 50 (25–65) min with Angelchik. Hospital stay was similar in both groups 8 (6–15) days.

Three patients underwent Angelchik removal for dysphagia, whilst no Nissen patient required revision. The patient functional outcome is detailed in the *Table* below, using Visick grading.

Time after operation	Angelchik		Nissen	
	V1+V2	V3+V4	V1+V2	V3+V4
3 months	18/25	7/25	22/25	3/25
6 months	16/23	7/23	19/22	3/22
12 months	14/20	6/20	17/20	3/20
24 months	6/10	4/10	7/8	1/8

These data show that, in a specialist unit, Nissen fundoplication is associated with a superior functional outcome to that of the Angelchik prosthesis for up to 2 years following surgery.

Cholecystectomy and gastro-oesophageal reflux

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Duodenogastric reflux is increased following cholecystectomy. The purpose of this study was to examine the effects of alteration of gastric pH on gastro-oesophageal reflux parameters in cholecystectomy patients. Forty-eight patients underwent endoscopy, oesophageal manometry and dual channel gastric and oesophageal pH monitoring. Patient groups were; normal ($n=14$), cholelithiasis pre-operative ($n=11$), post-cholecystectomy ($n=23$). Gastric pH >4, oesophageal acid score and lower sphincter pressure (LOSP) were compared. Results in the *Table* are expressed as mean ±s.e.m.

	Normal	Cholelithiasis	Cholecystectomy
Gastric pH >4	10·6 ±1·5	12·9±2·9	16·7±2·3*
Oesophageal score	6·72±0·9	29·2±1·4*	40·3±3·1*
LOSP (mmHg)	20·3 ±1·7	16·7±1·53	12·65±1·2**

*$p<0.05$; **$p<0.01$

There was a significant elevation in gastric pH postcholecystectomy compared to normals. Oesophageal acid exposure was higher in cholelithiasis patients and was exacerbated following surgery. This was associated with a significant fall in LOSP, the mechanism of which remains to be established.

Laparoscopic cholecystectomy and extracorporeal shock wave lithotripsy in the management of gallstone disease

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The recent introduction of laparoscopic cholecystectomy (LAPC) has revolutionized the surgical treatment of gallstone disease. However, it has also raised doubts about the future role of extracorporeal shock wave lithotripsy (ESWL) in the treatment of gallstones. In this study, we compared patients successfully treated with ESWL and dissolution therapy to patients treated by LAPC. Forty-nine out of 67 had successful clearance with ESWL while 30 out of 33 had successful LAPC. We evaluated treatment duration, recurrence rate (ESWL) and cost of treatment in both treatment modalities.

All patients had uncomplicated symptomatic gallstones. The inclusion criteria were similar in both groups, with the exception of patients with non-functioning gallbladders who were excluded from ESWL.

Criteria for comparison	ESWL	LAPC
Mean duration of treatment (days)	186 (30–540)	3 (2–6)
Mean time of work (days)	3 (1–5)	18 (3–42)
Major complication rate (%)	1	0
Recurrence (number of patients)	6	–
Estimated cost per patient including the failures and recurrences	£2045	£1015

These early results suggest that although ESWL is non-invasive with minimal morbidity, it has the disadvantage of being costly, with a high failure and recurrence rate. In contrast, laparoscopic cholecystectomy while requiring short-term hospital stay and debility seems to be a safe and an effective alternative with an advantage in terms of cost, and duration of treatment.

Demonstration of an enteric mucosal serotonin binding site by [^{3}H]ketanserin

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Although serotonin (5HT) induces intestinal secretion, the identification of a receptor for 5HT on mucosal cells has proved difficult. We demonstrated a putative 5HT$_2$ receptor on enterocytes by radioligand labelling with [^{3}H]5HT. By definition[1], [^{3}H]5HT has a low affinity for the 5HT$_2$ site and binding may be difficult to distinguish from non-specific background. Our hypothesis was that [^{3}H]ketanserin, a ligand specific for the 5HT$_2$ receptor[2] could label this site with higher affinity. To test this, a preparation of isolated, small intestinal mucosal cells from the guinea-pig was obtained by EDTA-chelation. Viability was 97±2 per cent by trypan blue exclusion and intracellular ATP and ADP levels were preserved in the isolated cells. Binding of [^{3}H]ketanserin to enterocytes was rapid, saturable, 65 per cent specific, stable and reversible. The reaction dissociation constant (K_d) was 5·0 nM, indicating high affinity binding. Binding was temperature-dependent and maximal at 37°C. Binding was inhibited by ketanserin and 5HT but not by the 5HT$_1$ antagonist 5HTP-DP, the 5HT$_3$ antagonist ICS 205-930 or by atropine, phentolamine or propranolol, indicating 5HT$_2$ site specificity. In conclusion, our results demonstrate high affinity binding of a selective 5HT$_2$ ligand to dispersed, viable enterocytes, supporting our hypothesis and substantiating the evidence for an enteric mucosal $5HT_2$ receptor.

1 Bradley PB, Engel G, Feniuk W, Fozard JR *et al.* Proposals for the classification and nomenclature of functional receptors for 5-hydroxytryptamine. *Neuropharmacol* 1986, **25**: 563–76

2 Leysen JE, Niemegeers CJE, Van Nueten JM, Laduron PM. [^{3}H]Ketanserin (R 41 468), a selective ^{3}H-ligand for serotonin$_2$ receptor binding sites. *Mol Pharmacol* 1982, **21**: 301–14

Mechanisms underlying raised portal pressure in portal hypertension

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It remains unclear why portal hypertension persists despite the presence of large portasystemic collateral vessels. The aim of this study is to examine the pathophysiology of portal hypertension in a rat model of cirrhosis. Severe decompensated cirrhosis was induced by 8–10 weeks lavage with carbon tetrachloride. Cardiac output and splanchnic blood flow were determined using a reference microsphere sample technique.

A hyperdynamic systemic circulation was present and splanchnic inflow significantly increased in the cirrhotic group.

	Cirrhosis ($n=6$)	Control ($n=6$)
Portal pressure (mHg)	15·1±1·5*	6·4±0·4
Cardiac output (ml min^{-1})	172±45	117±21
Splanchnic inflow (ml min^{-1})	13·2±1·3*	9·6±1·6
Total portal resistance (mmHg ml^{-1} min^{-1})	1·2±0·1	0·8±0·1

*$p<0·05$ (mean ±s.e.m.)

The serum level of glucagon which is known to increase splanchnic blood flow was measured in both groups. There was a twofold increase in glucagon in the cirrhotic group and this rise correlated with the level of portal pressure ($p<0·05$). This study explains why portal pressure remains elevated despite the presence of portasystemic collateral vessels and suggests that the rise in splanchnic inflow may be humorally mediated.

Raised pancreatic tissue pressures in chronic pancreatitis

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Pancreatic ductal hypertension may explain some of the pain of chronic pancreatitis, but increased pressure within the parenchyma might also be contributory. Tissue pressures were therefore measured intraoperatively in 17 patients with chronic pancreatitis and four controls with non-obstructing tumours or minimal disease. The technique involved direct fine-needle cannulation of the pancreas at various sites including the duct. The 23-gauge needle was connected via pneumohydraulic capillary infusion system to a signal amplifier and chart recorder. From three to six recordings, measuring resistance to infusión, were obtained at each site. In calcific pancreatitis, pancreatic tissue pressure (PTP: mean±s.e.m.) was substantially higher in all regions of the pancreas compared to controls: head (383±69 versus 19±5 mmHg, $p<0·01$), body (348±82 versus 38±21 mmHg, $p<0·01$) and tail (281±78 versus 11±3 mmHg, $p<0·05$). Elevations of PTP in regions of non-calcific pancreatitis did not achieve statistical significance: head (112±48 mmHg), body (120±34 mmHg) and tail (81±23 mmHg). Mean pancreatic ductal pressure in 10 patients (7 with calcific disease) was 13±5 mmHg. Differential pressure measurements within the pancreas helped determine the extent of resection in 11 patients with chronic pancreatitis, especially in 6 with very diffuse disease. The greatly increased tissue pressure in chronic pancreatitis, especially in the presence of calcification, suggests a possible 'compartment syndrome'.

Effect of duodenal juice on DNA index and cell proliferation in a model of oesophageal carcinoma

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Duodeno-oesophageal reflux increases the frequency of oesophageal cancer in carcinogen-treated rats[1]. Flow cytometry was used to study the effect of duodeno-oesophageal reflux on cell proliferation and nuclear ploidy in the oesophageal epithelium of this model. Sprague Dawley rats ($n=47$) underwent duodeno-oesophageal anastomosis to produce reflux of duodenal juice, or no operation. Following administration of the carcinogen (2,6-dimethylnitrosomorpholine), animals were killed at 12 and 20 weeks and their oesophagi examined for mucosal DNA content and proliferation rates (G2M+S phase per cent). At 20 weeks, 80 per cent of rats with carcinogen and duodeno-oesophageal reflux had established malignancy, a DNA index of 1·1 and proliferation rate of 12 per cent (normals 1·0 and 1·5 per cent, respectively, $p<0·01$). Three (17 per cent) showed aneuploidy. Those killed at 12 weeks showed no evidence of malignancy on histology, had diploid nuclei but a DNA index of 1·3 and proliferation rate of 13 per cent (greater than normal, $p<0·01$). Increased mucosal proliferation in rats with duodeno-oesophageal reflux precedes malignancy and may be related to the increased incidence of cancer in this reflux model.

1 Attwood SEA, Smyrk TC, DeMeester TR *et al.* Role of duodenal juice in the development of oesophageal adenocarcinoma. *Br J Surg* 1990, **77**: A693

Interstitial laser hyperthermia for liver cancer

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Experimentally, interstitial laser hyperthermia (ILH) using the neodymium yttrium aluminium garnet (Nd:YAG) laser produces well defined areas of tissue necrosis. Eight patients with a total of 13 hepatic metastases have been treated using ILH with a mean follow-up time of 5 months. Mean tumour diameter was 3 cm (1–6 cm). No patient had more than four metastases.

Under intravenous sedation, between one and four hollow 19-gauge needles, each bearing a laser fibre, were inserted percutaneously under ultrasound control into a selected metastasis. Each fibre emitted a power of 1·7–2·0 W from a Nd:YAG laser which was maintained for 500 s. There were no complications.

The treated metastasis was converted from a mixed echogenic to a hyperechogenic pattern on real time ultrasound monitoring. Treatment of small lesions was associated with a moderate rise of the aspartate transaminase within 24 h of therapy. Follow-up contrast-enhanced computerized tomography was performed at 6–8 weeks to assess the extent of non-enhancement and hence necrosis of the treated lesions. This revealed six metastases (five of which were ⩽2 cm in diameter) with necrosis in 50 per cent or greater of their respective volumes, two with necrosis in ⩽25 per cent of their volumes, and five metastases with no obvious necrosis (four out of the five were ⩾4 cm in diameter), two of which had increased in diameter. Disseminated disease has since emerged in two patients.

ILH is a safe technique for producing necrosis in small hepatic tumours and may have a role in their future management.

Effect of constituents of the coagulation factor complex II, IX, X on metastasis

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Depletion of coagulation factors II, IX, X by warfarin treatment inhibits, and injection of these factors enhances, metastasis in an animal model[1]. The aim of the study was to determine which individual factor or combination of factors is responsible for enhancing metastasis. Mtln3 mammary carcinoma cells (1×10^4) were injected i.v. into F344 rats either alone (group A, control), or together with purified human coagulation factors II, IX and X either alone or in different combinations (groups B–H, see *Table*). Animals were killed 17 days after injection and pulmonary seedlings assessed by the method of Wexler[2] The number of metastases in all experimental groups B–H was significantly higher than the control group A ($p<0·001$, ANOVA and Mann–Whitney *U* test) No significant differences were found between the individual groups B–H. Results are given in the *Table* as means ±s.e.m.

Number of pulmonary metastases in group							
A Control	B II	C IX	D X	E II+IX	F IX+X	G II+X	H II+IX+X
16 ±4	149 ±43	221 ±36	276 ±60	204 ±57	148 ±29	270 ±77	140 ±48

These results show that the coagulation factors II, IX and X enhance metastasis, individually as well as in combination This may indicate a common mode of action related to activation of the coagulation cascade

1 McCulloch P and George WD. Promotion of metastasis by a specific complex of coagulation factors may be independent of fibrin formation. *Br J Cancer* 1988. **58** 158–62.

2 Wexler H. Accurate identification of experimental pulmonary metastases. *Natl Cancer Inst* 1966; **96**: 641–5

Effect of suramin on suppression of natural killer cell proliferation by tumour products

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Current limitations of cancer immunotherapy with interleukin 2 (IL-2) may be partly due to the suppressive effect of tumour products on lymphokine-induced lymphoid activation Suramin is a selective cytokine antagonist which inactivates dimeric mesenchymal growth factors including transforming growth factor beta and fibroblastic growth factors

Mixed peripheral blood lymphocytes were activated by culture with 1000 U ml^{-1} IL-2. Parallel cultures also contained 10 per cent supernatant from LOVO cells (a colorectal cancer cell line) (LOVO-Sn), or 10 per cent LOVO-Sn and 200 $\mu g\ ml^{-1}$ suramin. After 96 h, expression of the antigens NKH1 (natural killer cells), CD3, CD4 and CD8 (T cells) and CD25 (IL-2 receptor, indicating cellular activation) was assayed by flow cytometry

Cultures with LOVO-Sn had fewer natural killer (NK) cells than those with IL-2 alone (mean 9·7 per cent, s.e.m 1·53 cf. 14 per cent, s.e.m. 0·96, $p=0·01$*) CD8+ cells were also diminished (mean 29·8 per cent, s.e.m 1·85 cf. mean 34·8 per cent, s.e.m 1·9, $p=0·002$*). The inhibitory effect of LOVO-Sn on NK cell proliferation was not apparent in the presence of suramin (mean 19·7 per cent, s.e.m 1·9, $p<0·001$*). A T cell decrease affecting mainly the CD4+ subset was apparent (mean 23·9 per cent, s.e.m 2·4 cf 50·8 per cent, s.e.m 2·2, $p<0·001$).

CD25 expression was lower in the presence of LOVO-Sn than in cultures with IL-2 alone ($p=0·015$) or cultures containing IL-2, LOVO-Sn and suramin ($p=0·05$).

Suramin can block some effects of tumour products on the immune system which may contribute to its recently discovered anti-cancer activity.

* Paired *t* test

Does significant liver to lung shunting occur in human colorectal liver metastases?

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Tumour shunting of cytotoxic drugs delivered into the liver reduces tumour cytotoxic drug levels and increases pulmonary and systemic toxicity We measured the ratio of technetium 99m labelled macroaggregated albumin (Tc-MAA) in liver and thorax following hepatic artery bolus administration

Sixteen patients with colorectal liver metastases in whom hepatic artery access has been established for regional cytotoxic infusion were studied. Two weeks after hepatic artery cannula insertion, 5 mCi of Tc-MAA with a median particle size of 30 μm (range 10 to 90 μm) were injected over 1 min Extent of liver volume replacement was assessed from CT scan by the point counting technique (Delesse's principle)

Liver shunting (median thorax liver count 1·4 per cent, range 0–4 per cent) did occur but did not exceed 4 per cent. There was a correlation ($r=0·671$, $P<0·01$) between percentage liver volume replacement (median 26 per cent, range 4 per cent to 60 per cent) and thorax liver count ratio

Liver to thorax shunting does occur in human colorectal liver metastases and this is related to extent of liver replacement Factors such as liver and tumour vascularity may be important The degree of shunting in colorectal liver metastasis is minimal and is unlikely to reduce tumour drug dose or increase systemic toxicity

Effects of urokinase and plasminogen activator inhibitor 2 on growth of a human tumour cell line

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Urokinase plasminogen activator (uPA) may act as an autocrine mitogen in some tumours We investigated whether recombinant plasminogen activator inhibitor 2 (rPAI2), a functional inhibitor of uPA, affected proliferation of the A431 cell line *in vitro* and *in vivo*

Cells were incubated in 24-well plates with protein-free medium or with 60 U ml^{-1} uPA or an equivalent concentration of rPAI2 At intervals, wells were fixed and stained, and cells counted in four high-power microscope fields at the centre of each well. Results are given in the *Table* as medians (range)

	Cells counted per well ($n=8$)		
Day	Control	uPA	rPAI2
0	162 (113–190)	167 (133–219)	152 (124–161)
1	247 (183–370)	288 (229–372)	292 (240–357)
3	426 (124–488)	568 (301–666)*	519 (343–822)*
5	1150 (82–1369)	1407 (662–1581)*	1032 (257–1685)
7	1282 (55–1779)	1343 (40–1859)	1363 (681–1973)

* $p<0·05$ compared with control (Mann–Whitney *U* test)

A possible mitogenic effect of uPA and rPAI2 was seen at 3 days, but the magnitude was small.

Nude mice, receiving 1×10^6 cells by intraperitoneal (i.p.) injection, were treated with daily i.p. injections as indicated for 16 days, then killed and the i.p. tumours weighed.

Tumour weight (g)		
Control ($n=9$)	uPA, 100 U ($n=9$)	rPAI2, 100 U ($n=10$)
2·066 (0·717–3·221)	1·946 (0·274–3·850)	0·29 * (0–1·151)

* $p<0·002$ compared with control (Mann–Whitney *U* test)

rPAI2 inhibited the growth of A431 i.p. xenografts in nude mice at a dose of 100 U daily, in a similar experiment treatment with rPAI2 at 5000 U daily had no effect on tumour weight compared with controls

Lipiodol as a potential vehicle for selective radiotherapy in liver metastases

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Lipiodol has been shown to be selectively retained within primary hepatic tumours following hepatic arterial injection It has subsequently been used as a carrier for various therapeutic agents We have studied the hepatic distribution in patients with colorectal liver metastases

Eleven patients undergoing selective coeliac angiography prior to 'port-a-cath' insertion underwent injection of 3 ml radiolabelled lipiodol (2 MBq ^{131}I) into the hepatic artery at the end of the procedure. At subsequent laparotomy 1–9 days later, biopsies were taken from normal liver and metastases and subjected to well-counting when the tumour:liver ratios were evaluated. Two patients with large metastases (>10 cm diameter) had low ratios. Of the remainder, at 24 h the median ratio was 1·5 (1·1–2·5, $n=5$) and at 3–9 days ($n=4$) the median ratio was 2·75 (1·5–63).

Three patients have undergone SPECT imaging which confirmed selective retention of lipiodol in small metastases, but no activity was detected in a large deposit (>15 cm) 10 days postinjection. Tumour:liver ratio was shown to be >2:1 at this stage in one patient.

This study suggests that lipiodol may be a useful therapeutic delivery agent to small colorectal liver metastases.

Duration of action of vasoconstrictor agents on liver blood flow

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Regional liver infusion of chemotherapy with vasoconstrictors increases the therapeutic advantage by reducing liver blood flow and increasing cytotoxic uptake. This benefit is reduced by reflex vasodilation and we have assessed the potential of three vasoconstrictor agents to produce a sustained reduction in liver blood flow.

Twenty-four male WAG rats, 200–300 g, were anaesthetized with halothane and nitrous oxide. The gastroduodenal artery was cannulated and angiotensin (40 μg), vasopressin (2 mU) or endothelin (1 nmol) were infused for 30 min. Liver surface blood flow was measured using laser Doppler flowmetry.

Group	n	Maximum fall in surface flow (%)	Duration of flow reduction (min)
Angiotensin II	8	31 ± 9·73	4·12 ± 1·20
Vasopressin	8	25 ± 5·71	8·68 ± 2·67
Endothelin	8	18 ± 5·60	20·83 ± 4·71

There was no significant difference between vasoconstrictor agents in maximum fall in surface flow. However, the duration of flow reduction was significantly ($p<0{\cdot}005$) longer with endothelin than angiotensin or vasopressin. Endothelin may be the most suitable vasoconstrictor agent for regional chemotherapy infusion.

Intermittent electrical stimulation of the gracilis neosphincter

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The gracilis sling procedure for faecal incontinence gives unpredictable results. Long-term electrical stimulation, conventionally at continuous low frequency (CLF), may improve neosphincter function by transforming the normally fast-twitch, fatiguable gracilis muscle into a slow-twitch, fatigue-resistant muscle. This study aimed to determine whether a different pattern of electrical activity, using intermittent bursts of higher frequency (IHF) stimulation also resulted in muscle transformation. Six patients stimulated by CLF (2 Hz) and six by IHF (15–25 Hz, on for 6–10 s, off for 1–10 s) were studied manometrically before and 8 weeks after stimulation. The pressure generated by the neosphincter at a range of frequencies was measured. The frequency which generated 50 per cent of the pressure achieved by the tetanic fusion frequency was determined and is shown in the *Table* as mean ± s.e.m.

	Frequency (Hz)		
	Pre-stimulation	8 weeks post-stimulation	Paired t-test
CLF	15·2 ± 2·4	9·8 ± 3·1	$p<0{\cdot}01$
IHF	15·7 ± 2·6	10·8 ± 2·1	$p<0{\cdot}05$

These results indicate that both patterns of stimulation result in transformation to a slow-twitch muscle. IHF stimulation achieves a degree of continence as soon as stimulation begins, which improves as transformation proceeds, as the off period is progressively shortened. This may enhance neosphincter function and reduce the need for defunctioning stomas in these patients.

Passage of shed intraluminal colorectal cancer cells across a sealed anastomosis

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Most local recurrence after colorectal cancer surgery is extraluminal. We present an experiment designed to establish whether free intraluminal cancer cells can pass through a freshly constructed airtight and watertight anastomosis and thereby potentially cause extraluminal recurrence.

Fischer rats ($n=18$) underwent descending colotomy with an air-tight and water-tight anastomosis. Test animals ($n=12$) received a 1 ml enema of 1×10^7 cells from a rat colorectal cancer cell line (RCC5) suspended in Dulbecco's modification of Eagle's medium (DMEM). For subsequent identification RCC5 cells were prelabelled with mouse monoclonal antibody (RCC 39·4) and a fluorescein rabbit anti-mouse conjugated antibody. Control animals ($n=6$) received a 1 ml enema of DMEM. At 1 h, animals were killed and the peritoneal fluid collected. Using flow cytometry, 10 000 cells were analysed from the peritoneal cavity of each animal. The number of fluorescent cells in control animals (representing background auto-fluorescence), was compared with the number of fluorescent cells in test animals (representing background auto-fluorescence + any leaked RCC5 cells).

	No. of fluorescent cells per 10 000 cells per animal
Control ($n=6$)	0, 0, 0, 3, 8, 8
Test ($n=12$)	0, 5, 10, 30, 36, 76, 78, 117, 193, 200, 406, 772

$p<0{\cdot}001$, difference of two proportions test

Free intraluminal cancer cells can cross a sealed anastomosis and may be a potential cause of extraluminal recurrence.

Abnormalities in the distribution of the extracellular matrix proteins, laminin and collagen type IV, in Hirschsprung's disease

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In vitro neurite outgrowth and neuronal survival are promoted by laminin, and neuronal migration is promoted by collagen type IV. This led to the hypothesis that Hirschsprung's disease (HD) could be the result of an abnormal extracellular matrix microenvironment in the affected bowel during embryogenesis.

Using indirect immunohistochemistry, we studied the distribution of laminin and collagen type IV in the bowel specimens of 8 HD patients (4 neonates and 4 infants) and 16 age-matched and site-matched controls from non-HD patients. In 8 HD specimens, the tissue studied was from the aganglionic (6), transitional (5) and proximal normoganglionic (8) zones.

Uniform distribution of laminin and collagen type IV was observed in the basement membrane of all control specimens. The semiquantitative abnormality in the distribution of these proteins in HD was: more intense immunoreactivities in the inner circular layer, diminishing with a gradient in the outer muscularis externa, in 6 of 6 aganglionic, 4 of 5 transitional and 3 of 8 normoganglionic sections. The qualitative abnormality of these proteins in HD was speckled immunofluorescence outside the basement membrane of the muscularis externa in all three zones of neonatal specimens only.

These findings support the microenvironment hypothesis of the pathogenesis of HD.

Effects of cisapride on the circular muscle of the human sigmoid colon *in vitro*

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Although the effects of cisapride on animal colon are well established, little information is availale about the effect on human colon We have examined the effect of cisapride on strips of normal sigmoid colon circular smooth muscle obtained from patients with rectal carcinoma, using a sucrose-gap technique. We have examined the effects on smooth muscle mechanical activity, membrane potential, membrane resistance and non-adrenergic, non-cholinergic inhibitory neuromuscular transmission, and the activity at serotonin receptors, adrenoceptors and P_2-purinoceptors

In tissues from ten patients (four male, six female, aged 45–78 years, median 61), cisapride at concentrations of 0 1 nM to 30 μM had no effect on: spontaneous mechanical or electrical activity, on membrane potential or resistance, or on non-adrenergic, non-cholinergic inhibitory junction potentials, which were evoked by electrical field stimulation (single pulses, 150 V, 0 08 ms, 0·033 Hz). Serotonin (0 1–1000 μM) and noradrenaline (3 and 30 μM) caused concentration-dependent hyperpolarization of the smooth muscle membrane, as did α,β-methylene ATP (30 μM). Cisapride (0·1 and 1 0 μM) caused concentration-dependent inhibition of responses induced by serotinin and noradrenaline, but not by α,β-methylene ATP

These results suggest that cisapride has no direct effect on the smooth muscle nor its inhibitory innervation, but that it can antagonize responses mediated by serotonin receptors (subclass as yet unknown) and adrenoceptors, but not P_2-purinoceptors, in the circular muscle layer of the human sigmoid colon.

Effect of vitamin D *in vitro* on rectal epithelial proliferation in familial adenomatous polyposis

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$1,25(OH)_2D_3$, the active metabolite of vitamin D, inhibits cell proliferation and induces cell differentiation in various human cancer lines. However its effect on rectal mucosa in patients at risk of developing colorectal carcinoma is unknown We have therefore investigated the effect of vitamin D on rectal epithelial proliferation in familial adenomatous polyposis using the stathmokinetic technique of metaphase arrest Sigmoidoscopic biopsies were obtained from macroscopically normal rectal mucosa in five familial adenomatous polyposis (FAP) patients with previous abdominal colectomy and ileorectal anastomosis. Samples were divided into 2 mm explants and established in organ culture with or without the addition of 1,25 $(OH)_2D_3$ (100 pM) to the culture medium. After 15 h, vincristine (0 6 μg ml^{-1}) was added to the medium, and samples were removed 1–3 h later for counting of metaphase arrests in microdissected crypts. Crypt cell production rate (CCPR) was determined by linear regression analysis of the accumulation of metaphases Vitamin D (100 pM) reduced CCPR by 52 per cent, from a control value of 8 75 ± 2 45 cells crypt^{-1} h^{-1} (mean + s e.m.) to 4 22 ± 1 28 cells crypt^{-1} h^{-1} ($p < 0\ 05$). This inhibitory effect suggests that vitamin D may have a protective role against the development of colorectal carcinoma in FAP

Congenital hypertrophy of retinal pigment epithelium expression in familial adenomatous polyposis families

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Congenital hypertrophy of retinal pigment epithelium (CHRPE) has been proposed as an important diagnostic marker for familial adenomatous polyposis (FAP) This was assessed in families with FAP in the West Midlands Sixty-eight people from 23 pedigrees were invited to attend for opthalmoscopy Only four people declined (from two pedigrees) The examination was performed without prior knowledge of their FAP status

Of 27 people known to be affected (group A), 22 had multiple CHRPE In 19 of these the lesions were bilateral In the remaining three cases the findings were considered significant because of the size or number of lesions. Only 6 out of 37 first-degree relatives, with a prior risk of 50 per cent but who had not yet developed polyps at the time of opthalmic examination (group B), had multiple CHRPE Of these six, one has since developed colonic polyps and another has been shown to carry the affected haplotype using polymorphic DNA probe analysis Results from group A gave a sensitivity of 81 5 per cent (22/27) Results from group B suggest a minimum specificity of 85 per cent (24/28) in our FAP population.

Although lower than previously reported, the incidence of CHRPE enables significant risk modification, potentially altering the frequency of subsequent bowel screening

Carcino-embryonic antigen levels in gallbladder bile and liver metastases from gastrointestinal tract cancer

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Owing to the relative insensitivity of currently available diagnostic modalities, 30 per cent of patients harbouring liver metastases from gastrointestinal cancer cannot be identified pre-operatively Carcino-embryonic antigen (CEA) is a sensitive serum marker of gastrointestinal cancer but a recent study has suggested that an elevated CEA level in gallbladder bile may be a more accurate indicator of hepatic metastases[1].

The aim of this study was to compare serum and gallbladder bile (obtained by intra-operative transhepatic gallbladder puncture) CEA levels in two groups of patients with gastrointestinal cancer, group A. proven liver metastases ($n = 7$) and group B, no operative or ultrasound evidence of metastases ($n = 8$) A control group of 10 elective cholecystectomy patients had undetectable serum and biliary CEA levels Results are shown in the *Table* as median (range)

	CEA (μg l^{-1})	
	Serum	Gallbladder bile
Group A	4·6 (1 2–663 0)	500 0 (12 2–3500 0)
Group B	4 0 (2 5–21·3)	20 4 (11 0–104 0)

These results confirm that gallbladder bile CEA levels are increased in the presence of hepatic metastases from gastrointestinal cancer As bile can be obtained pre-operatively by ultrasound guided percutaneous aspiration, there is potential for this relatively inexpensive technique to markedly influence therapeutic decisions

1. Yeatman TJ, Bland KI, Copeland EM III *et al* Relationship between colorectal liver metastases and CEA levels in gallbladder bile *Ann Surg* 1989, **210**: 505–12

Manipulation of regional drug delivery in an animal model of colorectal metastases using degradable starch microspheres and angiotensin II

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Using both embolization and pharmacological agents to enhance regional tumour targeting, we have achieved encouraging results treating patients with liver metastases Employing a rat model with similar haemodynamic characteristics to human tumour and a radiolabelled marker of similar molecular weight to adriamycin we have combined both approaches to see if they were synergistic

In animals with discrete liver tumours, [^{99}Tc]methylenediphosphonate (MDP) was administered intra-arterially alone or in combination with degradable starch microspheres (DSM) with or without angiotensin II Tumour to liver (T/L) distribution of MDP was measured at 1 and 90 min Results are given in the *Table* as median (range)

At 1 min, retention of MDP was significantly increased in both tumour and liver tissue in both treatment groups relative to controls, but the T/L ratio was unaltered At 90 min there was preferential retention of marker in tumour, most marked in the combination group.

	T/L ratio of MDP		
	Control	DSM	Angiotensin II + DSM
1 min	0·72 (0·1–6·2)	0·69 (0·1–4·2)	0·72 (0·2–2·2)
90 min	0·49 (0·2–1·1)	2·09* (0·1–3·6)	5·22** (1·9–11·4)

* > control ($p=0{\cdot}02$). ** > control + DSM alone ($p<0{\cdot}001$), Kruskal-Wallis and Mann–Whitney tests

We have previously established that angiotensin II does not enhance the T/L ratio at 90 min. These results suggest the combination of angiotensin II and DSM may be beneficial in maximizing chemotherapeutic delivery, and should be assessed in patient studies.

HPV type 16 DNA and anal squamous carcinoma in six countries

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An association between a sexually transmissible papillomavirus (HPV type 16) and anal squamous cell carcinoma (SCC) has been described in the UK and in the US. Genital papillomavirus infection and anal cancer occur throughout the world, this study examined the prevalence of HPV type 16 DNA in anal SCC from six countries.

Formalin-fixed, paraffin-embedded tissue specimens of anal SCC were obtained from Brazil (17), Switzerland (44), India (29), Poland (55), South Africa (28) and the UK (99). These specimens were examined for HPV type 16 DNA by high stringency DNA–DNA hybridization. The results were validated by using the polymerase chain reaction on a sample of thirty specimens.

Country	No. of cases	No. of cases positive for HPV16	Positive for HPV (%)
UK (multiple centres)	99	43	43
Brazil (Sao Paolo)	17	8	47
Switzerland (Geneva)	44	19	43
Poland (Warsaw)	55	19	35
South Africa (Cape town)	28	3	11
India (Madras)	29	1	3

These results show that anal SCC is associated with HPV type 16 in different geographical areas; although there is a significant difference ($p=0{\cdot}02$) in the prevalence of HPV16-associated anal cancer in India and South Africa compared with the prevalence in Poland, Brazil, Switzerland or the UK. These data suggest that since the prevalence of HPV-associated anal cancer varies from country to country other aetiological factors are likely to be involved in the pathogenesis of this tumour.

Significant excess of DNA adducts in the foregut of patients with familial adenomatous polyposis

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Duodenal neoplasms in patients with familial adenomatous polyposis (FAP) cluster around the ampulla, duodenal neoplasia is common but gastric neoplasia is rare. These observations suggest that bile enhances neoplasia by carrying carcinogens to target cells. A critical step in carcinogenesis is the reaction of carcinogens with DNA to form chemical adducts. Using DNA adducts as markers for carcinogens we investigated whether there are more adducts in FAP duodenum than in control duodenum and whether there are more adducts in duodenum than stomach.

We measured duodenal DNA-adducts levels by post-labelling with ^{32}P in 51 FAP patients and 30 controls. More FAP patients (49/51) than controls (24/30) had duodenal DNA-adducts ($p=0{\cdot}027$, Fisher's exact test) and relative adduct labelling (RAL: adducts/10^9 nucleotides) was higher in FAP patients than controls (medians, ranges: 15, 0–162; 7·5, 0–40, $p=0{\cdot}0002$, Mann–Whitney *U* test). We also measured RAL levels in paired biopsies from 31 FAP patients. Duodenal RAL was higher than gastric (medians, ranges: 15, 0–109; 8, 0–40; $p=0{\cdot}003$ Mann–Whitney *U* test). These results are consistent with the presence of DNA-reactive carcinogens in bile.

Altered mucosal proliferation in human colorectal neoplasia

D.A. Rew, C.S. Potten, M. Kellett, S. Roberts and I. Taylor, *University Surgical Unit, Southampton and Paterson Institute, Christie Hospital, The Cancer Research Campaign, UK*

One hypothesis of colorectal tumourigenesis is that altered mucosal crypt cell proliferation is a precursor to malignancy. Altered mucosal proliferation may occur in proximity to a tumour and in premalignant conditions, such as chronic inflammatory bowel disease and familial polyposis coli (FPC). Crypt cell proliferation in normal human colorectal mucosa has been described using *in vivo* bromodeoxyuridine labelling. Computerized quantitative histochemistry facilitates the detailed mapping and comparisons of crypt labelling in large numbers of specimens.

Twenty patients with primary colorectal cancers consented to receive a bolus injection of 250 mg bromodeoxyuridine between 2·4 and 16 h prior to conventional surgery. Mucosal strips were excised from resection specimens adjacent to (1–2 cm) and distant from (5–30 cm) the primary tumour. Mucosa at multiple sites from two patients with severe polyposis coli was also studied. Fifty longitudinal crypts per specimen were counted.

No differences were found in the pattern of peak labelling in mucosa close to or distant from tumours (mean LI 10·1 per cent). In contrast, a shift was seen in the peak labelling position from cell position 20 to 40 in all FPC mucosa. There were marked changes at the boundary between crypts and microadenomas.

Field change is unlikely to contribute to the development of neoplasia in normal colorectal mucosa. Subtle changes in FPC mucosal proliferation are detectable by this technique.

Pathological variables in colorectal carcinoma

G.T. Deans, M. Heatley, N. Anderson, K. Williamson, P. Hamilton, B.J. Rowlands, T.G. Parks and R.A.J. Spence, *Department of Surgery, The Queen's University of Belfast, Belfast, UK*

A study was performed to assess the reproducibility and relationship to survival of the pathological variables of Jass' classificaion[1]. All available histological material in 312 cases of colorectal adenocarcinoma were reviewed by an experienced pathologist with respect to a series of pathological variables. Twenty cases were reassessed by the same, and by a second pathologist. Log rank survival analysis and Kappa statistics were used to compare the prognostic significance and reproducibility of each variable.

Extent of tumour penetration, degree of differentiation, growth pattern, extent of fibrosis and venous invasion were related to patient survival ($p<0{\cdot}0001$, $p<0{\cdot}0005$, $p<0{\cdot}0005$, $p<0{\cdot}009$ and $p<0{\cdot}01$, respectively). Although the reproducibility of tumour penetration was good (Kappa = 0·825 and 0·929 for intra-observer and inter-observer variation, respectively), that for the other variables was fair or poor (intra-observer and inter-observer Kappa values for each of the other variables stated above being 0·57, 0·26, 0·37, 0·41; 0·29, 0·43, and 0·58, 0·64, respectively). Lymphocytic infiltration, although closely related to survival ($p<0{\cdot}001$) showed the greatest intra-observer (Kappa = 0·08) and inter-observer variation (Kappa = 0·05).

Although several pathological variables are related to survival many are poorly reproducible. Tumour penetration is the most significant and reproducible prognostic variable in colorectal cancer.

1 Jass JR, Love SB, Northover JMA. A new prognostic classification of rectal cancer. *Lancet* 1987; i: 1303–6.

Improvement in physiological function with enteral nutrition

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Intravenous nutrition (IVN) improves physiological function in depleted patients with acute inflammatory bowel disease[1]. The effect of enteral nutrition (EN) is unknown. The effect of nutritional repletion on physiological function was compared in 32 patients receiving two weeks of either IVN ($n=21$) or EN ($n=11$). All patients received equal amounts of protein and calories per kg body weight. Skeletal muscle function (grip strength) and six separate measures of respiratory function were assessed

With IVN, grip strength improved from 20·1 ± 10·1 kg (mean ± s.d.) to 24·3 ± 10·2 ($p < 0\cdot0005$), paired t test) and from 23·2 ± 8·1 to 26·4 ± 9·8, $p < 0\cdot01$) with EN Respiratory function improved significantly with IVN, but not with EN, e g the peak flow rate improved from 292 ± 136 l min^{-1} to 379 ± 137 ($p < 0\cdot001$, IVN) but by only from 352 ± 115 to 375 ± 121 (n s, EN). The improvement noted occurs maximally within 5 days after commencement of nutritional support.

In conclusion, nutritional support (IVN or EN) signficantly improves physiological function within 5 days The effect on respiratory function in EN patients appears to be less. The presence of the nasogastric tube is probably responsible for this.

1 Christie PM, Hill GL Effect of intravenous nutrition on nutrition and function in acute attacks of inflammatory bowel disease *Gastroenterol* 1990, **99** 730–6.

Monocyte lysosomal enzyme secretion in jaundice

W G Jiang, M C.A Puntis, (L E. Hughes), *University Department of Surgery, University of Wales College of Medicine, Cardiff CF4 4XN, UK*

Jaundice may cause damage to the reticuloendothelial system. We designed a study to investigate lysosomal enzyme secretion by monocytes in jaundice.

Twenty-two patients with obstructive jaundice and the same number of controls entered the study Purified peripheral blood monocytes were stimulated by phorbol myristate acetate (PMA), opsonized zymozan particles, or with plain culture medium The lysosomal enzyme *β-N*-acetyl-hexosaminidase activity released into the supernatant was measured, colorimetrically and expressed as a percentage of the total activity released from Triton-treated cells The plasma hexosaminidase was measured at the same time Results are given in the *Table* as median (interquartile range)

	Spontaneous (%)	PMA (%)	Zymozan (%)
Control	7·5	22·2	39·4
	(2·5–14·3)	(13·9–30·7)	(22·7–47·8)
Jaundice	20·3	28·7	41·2
	(14·2–23·2)	(23·9–40·0)	(34·8–47·1)
p*	$<0\cdot001$	$=0\cdot03$	$>0\cdot05$

* Mann–Whitney *U* test

The plasma hexosaminidase in jaundice was greatly increased (40·5 U l^{-1} against 13·5 U l^{-1} in control, $p < 0\cdot001$) There was a correlation between plasma enzyme and monocyte total lysosomal enzyme activity $r = 0\cdot528$, $p < 0\cdot01$). There was no relation between lysosomal enzyme and bilirubin

We conclude that in jaundice monocytes increase their spontaneous lysosomal enzyme secretion, which may account for the increased plasma hexosaminidase in jaundice

Generation of cytolytic tumour-infiltrating lymphocytes for gastrointestinal cancer therapy

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Adoptive immunotherapy with tumour-infiltrating lymphocytes (TIL) activated and expanded using interleukin 2 (IL2) is more effective than using adoptively transferred IL2-activated peripheral blood lymphocytes in patients with renal cancer and malignant melanoma

To determine whether such TIL could be expanded for clinical use in patients with gastrointestinal (GI) cancer we attempted to generate IL2-activated TIL from eleven primary or secondary GI tumours and six malignant effusions of GI origin The incidence of culture success, maximum-fold proliferation and cytotoxicity of these preparations were compared with those of TIL isolated from two renal cancers and four melanomas

TIl cultures were successfully established from four of the six melanoma/renal cell tumours but from only four of eleven GI tumours In contrast TL were expanded from all six malignant GI effusions Other results are given in the *Table* as mean (range)

Tumour origin	Renal/melanoma	GI tumour	GI effusion
Maximum proliferation	46·2 (1·6–100)	4·6 (1·6–22)	16·2 fold 1–39·1)
Cytotoxicity E·T ratio 50·1	50–70%	0–40%	30–77%

On flow cytometry, tumouricidal TIL were predominantly cytotoxic T-cells while non-cytolytic TIL were of helper T-cell phenotype

Compared with melanoma and renal carcinoma, TIL from primary or secondary GI cancers neither proliferate well nor exhibit high cytolytic capacity However, lymphocytes isolated from malignant GI effusions have potentially useful characteristics for adoptive immunotherapy

Effect of monocyte production of tumour necrosis factor in jaundice

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The monocyte is the main source of tumour necrosis factor (TNF) which is important in immune regulation and tumour biology However a systemic increase of TNF may be lethal[1] We have studied the TNF production in jaundiced patients.

Twenty patients with obstructive jaundice were studied with matched controls Purified peripheral blood monocytes were stimulated by lipopolysaccharide (LPS), and TNF in the culture supernatant measured by a L929 cell killing bioassay

TNF production (median, interquartile range) was 71·0 U ml^{-1} (37·0–618·0) in jaundice and 16·8 U ml^{-1} (5·2–27·8) in controls This was a significant difference by Mann–Whitney *U* test ($p = 0\cdot002$) There was no difference between male and female or between benign and malignant The TNF level was inversely correlated with plasma bile salt concentration ($r = -0\cdot603$, $p < 0\cdot001$) but not related to bilirubin level.

We conclude that monocytes produce more tumour necrosis factor in jaundice The level is not related to the depth of jaundice but bile salts may inhibit TNF production. We hypothesize that this increase may be harmful to this group of patients

1 Tracey KJ, Lowry SF, Fahey TJ *et al* Cachectin/tumour necrosis factor induces lethal shock and stress hormone responses in the dog *Surg Gynecol Obstet* 1987; **164** 415–22

Effects of balloon dilatation on canine ureteric physiology

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Balloon catheter dilatation of the ureter is a common procedure performed prior to ureteroscopy The effect on ureteric structure and peristaltic function is unclear

In 12 female mongrel dogs the effect of balloon catheter dilatation of a segment of upper ureter was compared with that of adjacent proximal and distal ureteric segments Via a flank incision, a 4 cm, 5 mm balloon catheter was inserted transcortically over a guide wire into the left upper ureter Ureteric segments were dilated to 10 atm for 3 min Motility of the dilated segments was measured prior to, and immediately postdilatation, and again after a 2 and 6 week recovery period A tunnelled subcutaneous nephrostomy tube was left indwelling in the renal pelvis, allowing chronic access to the collecting system for motility measurements and upper tract contrast studies

Immediately postdilatation, the dilated segment and proximal pelviureter showed a rise in baseline pressure from 4 ± 2·3 to 45 ± 4·6 mmHg, with associated loss of peristaltic activity. Distal ureteric pressure/motility was unaffected at this point At 2 weeks postdilatation motility of the dilated segment and distal ureter was significantly diminished Nephrostograms showed hydronephrosis, and dilated upper ureteric segments with extravasation in one animal At 6 weeks postdilatation, motility of the dilated segments, proximal pelviureter and distal ureter had returned to normal However in four of the ureters, the dilated segments showed persistent signs of impaired contractility These segments showed residual dilatation and histological evidence of chronic inflammation.

Balloon dilatation is associated with significant structural and functional disruption of the canine ureter. Pressure, duration and balloon diameter should be limited to the minimum necessary for the procedure required.

Requirements of activated murine T cells for arginine-derived nitric oxide for maximal DNA synthesis

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In neutrophils and macrophages arginine is a substrate for the production of the powerful bio-regulatory molecule nitric oxide (NO). We hypothesized that, since arginine is a known modulator of T lymphocyte function, it might be a substrate for NO production in these cells. Using murine cytotoxic (CTLL) and helper (HT2) T cell clones as a source of pure T cells, we demonstrated by a sensitive platelet aggregation bioassay that IL2-activated T cells produce NO. The functional requirements for this production were investigated in a microculture system and yielded similar results for both cell types. Without arginine, DNA synthesis is significantly reduced. 0.1 mM arginine in the culture medium restores proliferative responses and this correlates with increased production of specific NO end products (nitrites, nM/10^7 cells). N^G-monomethyl-arginine (NMMA, 0.1 mM), an inhibitor of NO production, significantly reduces DNA synthesis (*Table*), whilst exogenous NO (provided as sodium nitroprusside) increases it. Total lymphocyte protein synthesis is not affected by these culture conditions. Results are given in the *Table* as mean ±s.e.m. of eight separate experiments.

Culture conditions	CTLL [^{3}H]thymidine incorporation (counts min^{-1})	CTLL nitrite production
0.0 Arg	1349±203	91±7*
0.0 Arg+0·1 mM NMMA	206±15*	–
0.1 mM Arg	5167±405	214±22
0.1 mM Arg+0.1 mM NMMA	2128±408*	72±8*

* $p<0.05$ versus corresponding 0.1 mM arginine

In conclusion, following IL2 activation, murine T cells utilize arginine largely for NO production, which is required for DNA synthesis.

Correspondence

Endoscopic transthoracic electrocautery of the sympathetic chain for palmar and axillary hyperhidrosis

Sir

We read with great pleasure and satisfaction the article by Burne *et al.* (*Br J Surg* 1990, 77: 1046–49) concerning the endoscopic technique of thoracic sympathectomy for hyperhidrosis of the hands. Since 1987, we have seen about 100 cases. Our results are in agreement with the published results. However, our approach is slightly different. A small (1 cm) incision is made 1 cm under the clavicle 2 cm from the sternum through which a laparoscopic needle is introduced. A pneumothorax is established and, through the intercostal space, a urological resectoscope is introduced. The ganglions riding over the first, second and third ribs and the nerve between are coagulated. The procedure is completed by removing the CO_2 while the lungs are ventilated by 40 cmH_2O pressure. Like Byrne *et al* we do both sides at the same time and the total operation time is 30–40 min. A postoperative chest X-ray usually shows a 1–2 cm apical pneumothorax which disappears within one to two days. The patients usually leave hospital on the day after the operation.

Almost 100 per cent of patients are dry directly after the operation. On a follow-up questionnaire 80 per cent state good results and 15 per cent are improved. No one regretted the sympathectomy. Two complications were noted, one increasing pneumothorax and one silent bleeding, necessitating drains in 1 and 2 days respectively. No other major complications occurred. About 15 per cent complained of prolonged pain in the back. The rest were without complaint and back to work within 1–2 weeks.

The outcome of this simplified techique is excellent and as good as open surgery but with less postoperative morbidity. It is a cheap way of treating people suffering from a life-long handicap.

The experience of Byrne *et al* and ourselves can establish the endoscopic technique to perform thoracic sympathectomy as an effective and safe method, it should be learned and used by all surgeons who treat patients with palmar hyperhidrosis.

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Double linear stapling technique for oesophagojejunal anastomosis following total gastrectomy

Sir

We read with interest the article by T. L Zilling and colleagues (*Br J Surg* 1990, 77: 1375–8) concerning the use of linear stapling devices in oesophagojejunostomy following total gastrectomy.

We would like to endorse many of the observations made with respect to drawbacks of the circular stapling devices. In particular, following *en bloc* resection of the stomach bearing a cancer of the cardia with the lower oesophagus for proximal clearance, placing a purse-string suture presents technical difficulties as the oesophageal cut-end has retracted upwards behind the beating heart. Attempts at downward traction by stay sutures or by Babcock clamps might be met with tearing of the oesophagus, which is frequently very friable in these usually elderly patients.

We adopted the same double stapling technique described by the authors. However, recent years saw the almost exclusive use of a modification of the technique: the open end of the jejunal Roux loop is slid over the entire length of one fork of a GIA™ (US Surgical Corporation, East Norwalk, Connecticut, USA) instrument, which is then advanced into the posterior mediastinum alongside the back of the oesophagus. The other fork is passed up the oesophagus via an oesophageal stab wound. The instrument is closed, fired and withdrawn. With the ends of the two staple lines spread laterally by stay sutures, the jejunal end is stapled to the oesophagus by a TA 55® instrument. The lower oesophagus is amputated and specimen removed (*Figure 1*).

The modified technique saves one staple line and so obviates the potential risk of leakage from this staple line which might be thrust and weakened by the tip of the GIA fork when together they are insinuating into the posterior mediastinum. In addition, this method appears to be technically simpler, there is less danger of the TA instrument catching the jejunal mucosa at the mesenteric border by pulling up too much of the jejunal lip. Possibly, apprehension of the latter event led to inclusion of insufficient tissue at the terminal end of the GIA-stapled line between the TA jaws, resulting in the reported incidence of leakage.

During the stapling procedure, the oesophagus is retracted downwards by an assistant pulling on the specimen. Transection is followed immediately by remarkable ascent of the anastomosis to a level achievable only by a very troublesome circular stapling technique.

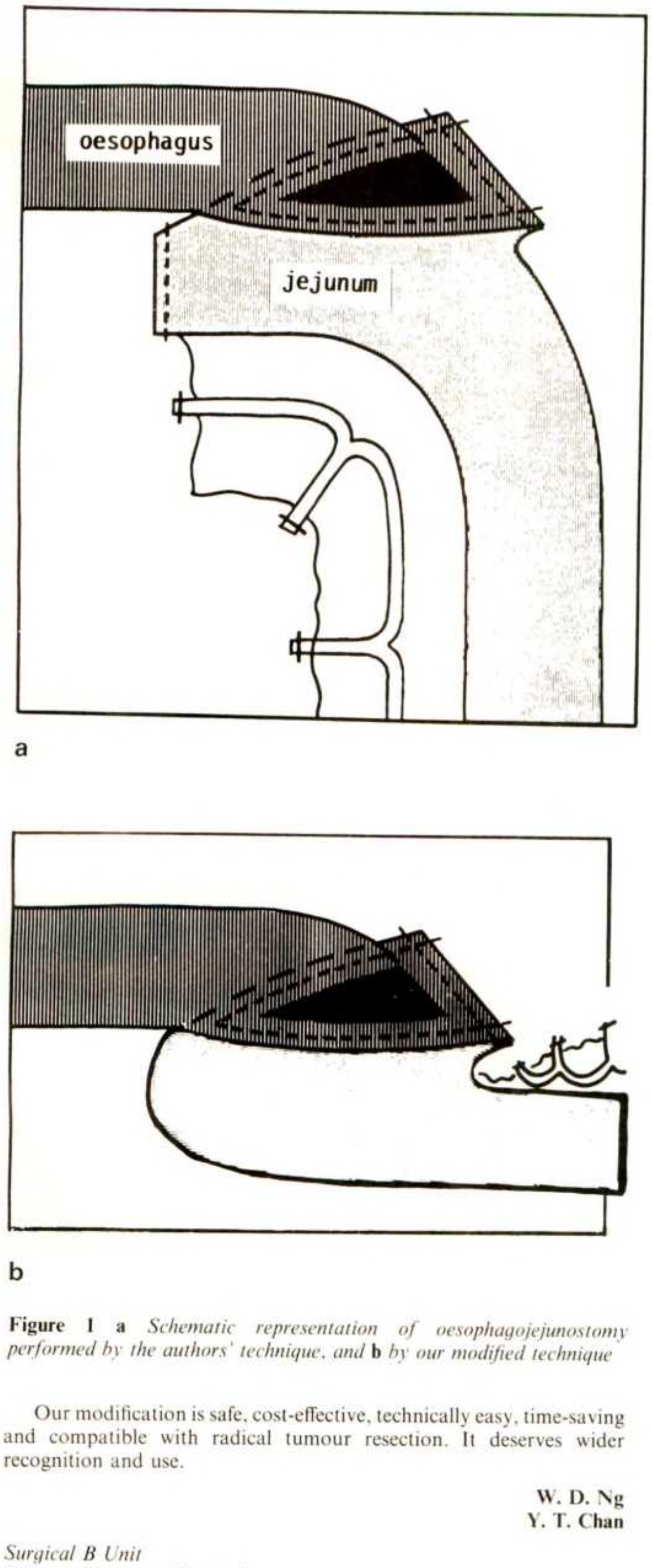

Figure 1 **a** *Schematic representation of oesophagojejunostomy performed by the authors' technique, and* **b** *by our modified technique*

Our modification is safe, cost-effective, technically easy, time-saving and compatible with radical tumour resection. It deserves wider recognition and use.

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Surgical management of primary hyperhidrosis

Sir

My surgical training began when vascular surgery had little to offer apart from sympathectomy and modified operations were also done, with doubtful benefit, for non-vascular disorders such as Hirschsprung's disease and essential hypertension. So we saw and did a great many sympathectomies. Primary hyperhidrosis is almost the only condition in which the operation has stood the test of time and Moran and Brady's review (*Br J Surg* 1991; **78**: 279–83) is timely and useful.

May I add a couple of technical suggestions. During lumbar sympathectomy removal of the chain can lead to serious bleeding from damage to lumbar veins crossing in front, particularly on the right. It is safer and just as effective to destroy the exposed chain between L2 and L4 with the surgical diathermy. There is no need to remove it and it does not regenerate.

For upper thoracic sympathectomy by the cervical approach, depression of the cervial pleura is a key step. The risk of tearing the pleura is much less if a pack is used to strip down the pleura. The suprapleural membrane is first broken with a finger, easiest near the medial end of the first rib. An opened out surgical swab can then be poked through the hole and packed in until it completely disappears into the suprapleural cavity. When the malleable retractor is then introduced, the pleura will already have been pushed down out of the way. But remember to extract the swab at the end.

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Abdominal wall dehiscence following Ramstedt's operation

Letter 1

Sir

Harvey *et al.* (*Br J Surg* 1991; **78**: 81–2) record a remarkably high incidence (6·7 per cent) of wound dehiscence in their series of Ramstedt's pyloromyotomies. Reviews of pyloromyotomy series in the United Kingdom revealed a wound dehiscence incidence of 0–5 per cent with the majority being under 2 per cent[1,2].

Their statement that mass closure has not been assessed in infants is patently incorrect. A large study comparing layered *versus* mass closure of abdominal wounds in infants and children demonstrated a very low incidence of wound failure in either group (1·6 per cent for layered closure and 0·4 per cent for mass closure, with no statistically significant difference between the two groups), and concluded that either method yields good results and non-absorbable sutures are unnecessary[3].

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Letter 2

Sir

Harvey *et al.* (*Br J Surg* 1991; **78**: 81–2) reported a wound dehiscence rate of 6·7 per cent for pyloromyotomy performed through a transverse incision which presumably either divided the right rectus abdominal muscle transversely or split it vertically. Many British series record dehiscence rates of 1–5 per cent for these types of incision[1–3]. From the USA in 1940, Robertson[4] reported the virtual elimination of this complication by resort to the right upper quadrant grid-iron incision. Using a slightly modified technique, i.e. through a transverse skin crease incision, this approach has given satisfactory results in the UK[3,5].

For more than a decade I have invariably used mass closure with polyglycolic acid for all transverse muscle cutting incisions in infants and children. As in adults, it is vitally important to insert the sutures well away from the wound edges but inexperienced surgical trainees have a tendency to take proportionately tiny 'bites' when operating upon neonates. If uncorrected this inappropriate technique results in dehiscence. Mass closure in infants has been investigated and gives satisfactory results when properly performed[6].

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Letter 3

Sir

I read the paper by Harvey *et al.* (*Br J Surg* 1991; **78**: 81–2) with interest, particularly since they quote my previous publication[1].

I stated quite clearly in this paper that the problem of burst abdomen is preventable and I quoted the work of Jenkins[2] for those who wish to achieve this ideal. For over 10 years I have applied Jenkins' technique to abdominal closure in children with the same excellent results that he obtained in adults. The only modification has been to use absorbable monofilament suture materials instead of non-absorbable. As I have stated elsewhere[3] whether layered or mass closure is used is irrelevant; it is adherence to Jenkins' principles which is crucial. The authors' conclusion regarding chromic catgut is no surprise; indeed the only surprise is that anyone is still using catgut for abdominal closure.

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Cholecystectomy through a 5 cm subcostal incision

Sir

We read with interest the paper by O'Dwyer *et al.* (*Br J Surg* 1990; **77**: 1189–90) and would like to support their views on mini-cholecystectomy.

Between 1 March 1990 and 31 December 1990 we considered mini-cholecystectomy in 32 consecutive patients undergoing surgery for symptomatic gallstones. The operation was impracticable in two patients due to gross obesity and in a third conventional cholecystectomy was performed because of insufficient surgical assistance. Of the remaining 29 patients, 20 were women and 9 were men. Their mean age was 53·2 years (median 55 years, range 22–83 years). Five patients presented with acute complications of cholelithiasis: acute cholecystitis (3 patients); calculus obstructive jaundice (1 patient); and pancreatitis (1 patient). Endoscopic retrograde choledochopancreatography (ERCP) and sphincterotomy were performed in the latter two cases before cholecystectomy. In 14 cases the principal surgeon was a Registrar. A Consultant assisted with six of these and was the principal operator in a further eleven cases. The remaining operations were performed or assisted by a Senior Registrar. Results obtained from 29 mini-cholecystectomies are shown in the *Table*.

	Mean	Median	Range
Wound length (cm)	5·7	6·0	5–10
Operating time (min)	46	45	30–90
Postoperative parenteral analgesia (doses)	4·1	4·0	0–8
Length of postoperative stay (days)	3·0	3·0	2–6

Three complications were recorded, two patients suffered urinary retention which settled after 36 h of urethral catheterization. One patient sustained a 2 mm iatrogenic injury to his common bile duct which was recognized and repaired with two fine absorbable sutures after the wound was extended to 10 cm. No T tube was used as the patient had previously undergone ERCP and sphincterotomy. The patient was discharged six days after surgery.

These findings support those of O'Dwyer *et al.* and confirm that cholecystectomy performed through a small incision is feasible and followed by a shorter recovery time than conventional cholecystectomy. Also, the results compare favourably with those reported for laparoscopic cholecystecomy[1–3]. Total wound length is a little longer for mini-cholecystectomy (5·7 cm *versus* 4·5 cm) but postoperative analgesia requirement is almost identical. Patients can expect to go home on the second or third postoperative morning after mini-cholecystectomy; one day later than in some reports for laparoscpic cholecystectomy. However, counterbalancing this is a 30–50 per cent saving in operating theatre time with mini-cholecystectomy. Mini-cholecystectomy also has the advantage that it neither requires expensive new equipment nor the acquisition of novel skills by the surgeon. Our experience shows that surgeons, familiar with conventional cholecystectomy, can change their technique easily to meet the demands of a minimal approach and perform the procedure in approximately equal time. Laparoscopic cholecystectomy requires substantial new skills and may be accompanied by a higher incidence of serious morbidity[4]. Such conclusions lead us to suggest that mini-cholecystectomy rather than conventional cholecystectomy is the standard by which alternative methods for treating symptomatic gallstones should be judged.

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Radiocephalic fistula in vascular access

Letter 1

Sir

I would like to point out a mistake in a leading article by Ryan and Dennis (*Br J Surg* 1990; **77**: 1321–1) in their description of the operative procedure: 'A transverse incision is made through the skin and subcutaneous tissue at the level of the head of the radius'.

I feel that where the incision is made is over the lower end of the radius The head of the radius is in relation to the capitulum and is proximal.

Therefore, the mistake has been made in describing the location of the incision in relation to the part of the radius. The incision should be described as a transverse incision over the lower end of the radius and not over the head as described

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Author's reply

Sir

Mr Mistry is of course absolutely correct The sentence in question should read 'a transverse incision is made through the skin and subcutaneous tissue at the level of the distal radius' We are grateful to Mr Mistry for pointing this out

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Letter 2

Sir

The leading article by Ryan and Dennis (*Br J Surg* 1990, 77 1321–2) describes in some detail the technical aspects of fistula creation. The authors state that 'if the surgeon prefers the anastomosis can be fashioned in a side-to-side manner. However, the distal venous limb should be ligated on completion of the anastomosis to obviate the complication of venous hypertension of the hand' Adjuring surgeons to ligate the distal venous limb of a side-to-side fistula is misguided. Studies of side-to-side fistulas indicate that there is rarely excessive flow in the distal limb at the time of fistula creation[1]. The distal segment of cephalic vein also serves as a useful needling site for the patient training for home or satellite dialysis. Venous hypertension of the hand usually develops at a late stage when the majority of fistula flow is directed distally following stenosis within the proximal venous limb of the fistula[2] The stenotic problems can be corrected by either balloon angioplasty, patch angioplasty, interposition grafting or refashioning of the fistula with an end-to-end side configuration more proximally in the limb[3] Venous hypertension may therefore be a useful indicator of more proximal problems allowing the fistula to be salvaged. In contrast, with an end-to-side anastomosis, the first sign of a problem may be presentation with a thrombosed fistula.

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Stercoral perforation of the colon

Sir

We read with interest the comprehensive review by Serpell and Nicholls (*Br J Surg* 1990, 77 1325–9). The authors referred to a variety of ingested substances, including analgesics, whch cause constipation and are important in the aetiology of stercoral perforations. Only a small percentage of constipated patients develop this complication and it is likely that other factors are involved A decrease in resistance of the colonic mucosa to local trauma and subsequent bacterial invasion of the bowel wall may be important.

We have recently managed 3 constipated patients who developed histologically proven stercoral perforations of the rectosigmoid colon while ingesting non-steroidal anti-inflammatory drug medications (NSAIDs) for painful musculoskeletal disorders These patients had taken either indomethacin, naproxen, or a sustained-release preparation of ketoprofen, for 6, 8, and 12 months before their admission with faecal peritonitis. Although the upper gastrointestinal side-effects of NSAIDs have been widely publicised, their effects on the larger bowel have only recently been recognized These drugs are all inhibitors of prostaglandin synthetase activity and it has been suggested that a reduction in mucosal prostaglandins may, by abolishing a 'cytoprotective' effect, compromise intestinal integrity, resulting in an increased susceptibility to transmucosal migration of luminal toxins[1]

Evidence from a comprehensive retrospective review suggests that 26 per cent of patients admitted with perforation and haemorrhage of the lower bowel are taking NSAIDs compared with 12 per cent of matched controls[2]. The authors of the review remarked on the similarity between stercoral perforations and perforation of colonic diverticula and an association has been reported between NSAIDs and the septic complications of diverticular disease[3].

Surprisingly anti-inflammatory drugs have been mentioned infrequently in patients developing stercoral perforations Certainly less than would be expected as these lesions usually occur in an elderly population for whom NSAIDs are widely prescribed. Perhaps this anomaly may be due to a failure to document these commonly prescribed drugs particularly if a causal association is not considered

When slow-release NSAID medications become more widely available without prescription constipated elderly patients may be at special risk

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Book reviews

Atlas of normal and variant angiographic anatomy

Saadoon Kadir 260 × 180 mm Pp 529. Illustrated 1991 Philadelphia W. B. Saunders. £59.00.

The principal author of this book has been assisted by eight others, almost all of whom practise in the USA. The work encompasses both arterial and venous angiography in almost equal detail, plus a small section on the lymphatics. The 18 chapters are divided into sections: arterial system of the trunk and extremities, venous system of the trunk and extremities, arterial and venous anatomy of the reproductive organs, arterial and venous system of the viscera, arterial and venous anatomy of the head, and the lymphatic system. The book contains nearly 500 angiograms backed up by nearly 100 line drawings, occasional magnetic resonance images, computed tomograms and the odd clinical photograph.

The volume is quite rightly called an 'atlas', it is a superb collection of angiograms showing normal and variant anatomy, explained by a crisp text with many tables describing the incidence of certain variant features. It is the attention to variation from the norm that makes this book unique and is, indeed, its raison d'etre. The depth of description devoted to most regions is appropriate to the overall length of the volume, the only exception being the lymphatic system which seemed rather short.

This is a reference work. While it is not a book that most surgeons will consider for personal purchase, those with a major interest in vascular surgery should consider seriously whether their unit library is complete without it.

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Laparoscopic Biliary Surgery

A. Cuschieri, G Berci 280 × 225 mm Pp. 101 + ix Illustrated 1990 Oxford: Blackwell Scientific Publications £39.50

At the present time there is an uncritical euphoria about laparoscopic cholecystectomy. It is therefore important and practical to have an authoritative and detailed guide on all aspects of the operation. This attractive book combines the skills and experience of acknowledged experts from both sides of the Atlantic.

The book rightly starts with an emphasis on adequate training before operating on humans because, at present in Britain, there are no restraints on a surgeon performing a new operation without any training or experience. The authors recommend familiarity with bench top simulators and anaesthetised animals. In the USA and central Europe the latter is allowed, but in Britain it is not except as part of a research project. British surgeons then have to make do with fresh animal livers and gallbladders but thin walled gallbladders and oozy livers are more appropriate than a bunch of grapes and uncooked chicken breasts[1] (p. 4).

The next section discusses instruments and the theatre arrangements. Each step of the operation is described in detail and each possible complication is faced and its solution given. This is a refreshing change from descriptions which skate over the problems and the authors show commendable calm when faced with a bleeding cystic artery! (p. 185)

The book's layout is uncluttered and it is well illustrated with colour and black and white photographs and many line drawings. The quality of the illustrations is high apart from one or two in which the focus or colour are poor and, unfortunately, the lighting in the black and white photograph of the operation in progress makes it look like an underground bunker during the war.

The section on contraindications is important because some surgeons seem to think that because a technique *can* be done it *should* be done whatever the risks or time under anaesthetic. It is good to see the leaders in the field readily prepared to change direction if there is an increased risk to the patient. However, a gallbladder wall thickness over 4 mm is not included although it is regarded as a contraindication by surgeons on the continent of Europe.

The chapter on laparoscopic *cholecystostomy* is less satisfactory as it combines a number of different techniques, without clear guidance, but perhaps it is too early to assess the whole concept of treatment of gallstones without removing the gallbladder.

The book's overriding message is that this new operation should be introduced in a planned, thoughtful, responsible and well audited way, but unfortunately financial, commercial and media pressures make this increasingly difficult. Surgeons can easily become obsessed with a technique and forget the patient and the aim of treatment. If problems do occur, as they will, the blame certainly cannot be laid at the door of Professor Cushieri and Dr Berci or the publishers of this excellent book.

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Review of Diagnosis of Acute Abdominal Pain (2nd edition)

F T de Dombal 222 × 142 mm. Pp. 259 + xiv. Illustrated 1990 Edinburgh Churchill-Livingstone £19.95 Hardback

Many excellent monographs already exist on the subject of the acute abdomen and everybody has their favourite. This latest text has a very 'chatty' style and is very readable, but I feel it is too long for the audience it addresses, namely medical students and junior surgeons.

The first half of the book was generally excellent. I was concerned, however, with the description of rebound tenderness, where the examining hand is pressed into the abdomen for 30 to 60 seconds and then, without warning, the hand is suddenly removed to above skin level. Such overzealous attempts to elicit rebound tenderness inflicts unnecessary suffering, and light percussion of the abdominal wall which is not mentioned in this text is, in my view, a better way of assessing whether the peritoneum is inflamed. The discussion of controversies such as the value of the white count and which radiological investigations are of value in the acute abdomen are well presented.

The second half of the book deals with conditions which cause abdominal pain and looks at the problems encountered in elderly patients, children and young women. I thought the same information could have been presented in half the space and there are some important omissions, there was no mention of the Ranson or Imrie criteria or the value of the APACHE II score in the prognosis of acute pancreatitis, the section on laproscopy is very short, in keeping with the author's acknowledged bias against this investigation, and there is no mention of peritoneal cytology.

Mr de Dombal tells us that his favourite book of all time is '*How to Play Your Best Golf All The Time*'. Considering the book in this context, his drive is good but he takes too many shots thereafter to get the ball into the hole.

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Notices and announcements

6–10 June 1991
American College of Cryosurgery
12th Annual Scientific Meeting
La Jolla, California, USA
Information American College of Cryosurgery, Attn. Michael Thompson, PO Box 3116, Evanston, IL 60204-3116, USA

9–12 June 1991
Fifth International Conference on Malignant Lymphoma
Lugano, Switzerland
Information: F Cavalli, Division of Oncology, Ospedale San Giovanni, 6500 Bellinzona, Switzerland

19–22 June 1991
73rd Annual Meeting of The Endocrine Society
Washington, D.C., USA
Information The Endocrine Society, 9650 Rockville Pike, Bethesda, MD 20814, USA

4–5 July 1991
74th Meeting of the Surgical Research Society
Lancaster, UK
Information Professor J. R. Farndon, Department of Surgery, University of Bristol, Bristol BS2 8HW, UK

4–6 July 1991
Symposium on Operative Endoscopy & Laser
Leuven, Belgium
Information Mrs Vandepoel, U Z Sint-Pieter, Brusselsestraat, 69, 3000 Leuven, Belgium

11–13 July 1991
XVIth International Update on Liver Disease
London, UK
Information. Professor Neil McIntyre, Academic Department of Medicine, Royal Free Hospital, Pond Street, London NW3 2QG, UK

12–13 July 1991
Hong Kong Surgical Forum
Hong Kong
Information Vera Fung, Department of Surgery, University of Hong Kong, Queen Mary Hospital, Hong Kong

14–16 July 1991
Techniques in Pulmonary and Oesophageal Surgery
Liverpool, UK
Information Mr R. J. Donnell, Cardiothoracic Centre, Broadgreen Hospital, Thomas Drive, Liverpool L14 3LB, UK

5–16 August 1991
European Postgraduate Summer Course in Practical Support of the Seriously Ill
Southampton, UK
Information Mr B. Moran, Department of Human Nutrition, University of Southampton, Bassett Crescent East, Southampton, SO9 3TU, UK

25–31 August 1991
International Surgical Week
Stockholm, Sweden
Information Scientific Secretariat, 155, Hauptstrasse 63, PO Box 411, CH-4153, Reinach BL1, Switzerland

1–6 September 1991
6th World Congress in Ultrasound
Copenhagen, Denmark
Information Spadville Congress Service, Sommervaj 3, DK-3100 Hornbaek, Denmark

4–6 September 1991
Oxford 1991, Graft Infiltration Meeting
Oxford, UK
Information Catherine Hughes, Nuffield Department of Surgery, John Radcliffe Hospital, Headington, Oxford OX3 9DU, UK

4–6 September 1991
1st European Conference on Advances in Wound Management
Cardiff, UK
Information· Christine Jones, Macmillan Conferences, 4 Little Essex Street, London WC2R 3LF, UK

9–13 September 1991
11th Congress of the European Association for Cranio-Maxillo-Facial Surgery
Innsbruck, Austria
Information Professor Dr R Fries, A-4040 Linz, Pferdebahnpromenade 17, Austria

19–20 September 1991
Tissue Viability Society Autumn Conference
London, UK
Information Mr J Gisby, Tissue Viability Society, Wessex Rehabilitation Association, Odstock Hospital, Salisbury, Wilts SP2 8BJ, UK

20–23 September 1991
60th Annual Meeting of the Royal College of Physicians and Surgeons of Canada
Quebec City, Quebec, Canada
Information Anna Lee Chabot, The Royal College of Physicians and Surgeons of Canada, 74 Stanley, Ottawa, Canada K1M 1P4

2–4 October 1991
12th International Symposium on Computer Assisted Decision Support & Database Management in Anesthesia, Intensive Care and Cardiopulmonary Medicine
Rotterdam, The Netherlands
Information Dr Omar Prakash, Thorax Centre, Erasmus University, 3000 DR Rotterdam, The Netherlands

7–10 October 1991
5th Congress of the European Society for Organ Transplantation
Maastricht, The Netherlands
Information. 5th ESOT Congress, Conference Agency Limburg, University Hospital Limburg, PO Box 1918, 6201 BX Maastricht, The Netherlands

9–12 October 1991
Principles of Colon and Rectal Surgery
Minneapolis, Minnesota, USA
Information Continuing Medical Education, University of Minnesota Medical School, Box 202 UMHC, 420 Delaware Street Southeast, Minneapolis, Minnesota 55255, USA

7–9 November 1991
3rd Combined Meeting of the Nederlandse Vereniging voor Thoraxchirurgie and the Deutsche Gesellschaft für Thorax-, Herz- und Gefässchirurgie
Maastricht, The Netherlands
Information Organizing Secretariat, Conference Agency Limburg, University Hospital Maastricht, PO Box 1918, 6201 BX Maastricht, The Netherlands

7–10 November 1991
XVII European Society for Medical Oncology Conference
Lyon, France
Information Michel Clavel, MD, XVII Congress ESMO, CLB, 28, rue Laennec, 69373 Lyon Cedex 08, France

12–14 November 1991
1st European Conference on Tissue Banking and Clinical Application
Berlin, Germany
Information Mr Rudiger von Versen, German Central Tissue Bank, ITT, Medical Faculty (Charite), Humboldt-University Berlin, Schumannstr 20/21, D-1040 Berlin, Germany

17–23 November 1991
Surgery of the Pancreas, Liver and Biliary System
Edinburgh, UK
Information Courses Department, The British Council, 10 Spring Gardens, London SW1A 2BN, UK

3-5 December 1991
6th International Workshop on Therapeutic Endoscopy
Hong-Kong
Information Dr J W. C. Leung, Department of Medicine, The Chinese University of Hong-Kong, Prince of Wales Hospital, Shatin, Hong-Kong

12–13 December 1991
1st EEC Conference on Pain Research
Brussels, Belgium
Information M Staquet, Rue Heger-Bordet, 1, B-1000-Brussels, Belgium

3–7 May 1992
7th International Congress of Mastologie
Rhodes, Greece
Information E. Soutas, Public Relations Center Ltd , 102 Michalakopoulou Street, 115 28 Athens, Greece

SURGERY

CONTENTS, MAY 1991

Volume 109, Number 5

Official Publication
SOCIETY OF UNIVERSITY SURGEONS, CENTRAL SURGICAL ASSOCIATION,
and **AMERICAN ASSOCIATION OF ENDOCRINE SURGEONS**

ORIGINAL COMMUNICATIONS

Page 567 **Volume tests for chronic venous insufficiency: An appraisal**
E. Converse Peirce II, MD, Konan Chiang, MD, *and* Harry Schanzer, MD

575 **Fifteen-year results of ambulatory compression therapy for chronic venous ulcers**
John C. Mayberry, MD, Gregory L. Moneta, MD, Lloyd M. Taylor, Jr., MD, *and* John M. Porter, MD

582 **Serosal invasion as the single prognostic indicator in stage IIIA (T3N1M0) gastric cancer**
Shun'ichi Abe, MD, Morio Shiraishi, MD, Saburou Nagaoka, MD, Hiroshi Yoshimura, MD, Dipok Kumar Dhar, MD, *and* Teruhisa Nakamura, MD

589 **Development of a computer-aided surgery system: Three-dimensional graphic reconstruction for treatment of liver cancer**
D. Hashimoto, MD, PhD, T. Dohi, DEng, M. Tsuzuki, MD, PhD, T. Horiuchi, DEng, Y. Ohta, MS, K. Chinzei, MS, M. Suzuki, BS, *and* Y. Idezuki, MD, PhD

597 **Total parenteral nutrition and tumor metastasis**
Michael H. Torosian, MD, *and* Robert B. Donoway, MD

602 **Somatosensory-evoked potentials during carotid artery surgery: Experience in 400 operations**
Hans Schweiger, MD, Hans-Dieter Kamp, MD, *and* Michael Dinkel, MD

610 **Acute lower limb ischemia: Failure of anticoagulant treatment to improve one-month results of arterial thromboembolectomy. A prospective randomized multi-center study**
Lennart Jivegård, MD, PhD, Jan Holm, MD, PhD, David Bergqvist, MD, PhD, Claes-Göran Björck, MD, PhD, Hilding Björkman, MD, Ulf Brunius, MD, PhD, Göran Claes, MD, PhD, Jan Hammarsten, MD, PhD, Bengt Jernby, MD, Peter Konrad, MD, PhD, Bengt Lindblad, MD, PhD, Leif Lindblad, MD, PhD, Gunnar Plate, MD, PhD, Leif Spangen, MD, PhD, *and* Tomas Troeng, MD

617 **Thromboprophylaxis in patients with hip fractures: A prospective, randomized, comparative study between Org 10172 and dextran 70**
D. Bergqvist, MD, PhD, K. Kettunen, MD, PhD, H. Fredin, MD, PhD, P. Faunø, MD, O. Suomalainen, MD, PhD, S. Soimakallio, MD, PhD, P. Karjalainen, MD, C. Cederholm, MD, L. J. Jensen, MD, T. Justesen, MD, *and* J. C. J. Stiekema, MD

623 **Complete external iliac artery disruption after percutaneous aortic valvuloplasty in two young children: Successful repair with hypogastric artery transposition**
Dolores F. Cikrit, MD, Mary Alice Helikson, MD, W. Kirt Nichols, MD, *and* Donald Silver, MD

627 **A simple infusion method for measurement of intraoperative peripheral vascular runoff resistance**
Sadettin Karacagil, MD, PhD, Murat Bayazit, MD, Staffan Bowald, MD, PhD, Bo Almgren, MD, PhD, *and* Ingvar Eriksson, MD, PhD

Mosby
Year Book
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633 **Assessment of aortoiliac obstructive disease by Doppler spectrum analysis of blood flow velocities in the common femoral artery at rest and during reactive hyperemia**
W. N. J. C. van Asten, PhD, W. J. Beijneveld, MD, B. R. Pieters, MD, H J. J. van Lier, MSc, P. F. F. Wijn, PhD, *and* S. H Skotnicki, PhD, MD

640 **Serum transthyretin levels in patients with burn injury**
L. Cynober, PhD, O. Prugnaud, PhD, N. Lioret, MD, C. Duchemin, PharmD, R. Saizy, MD, *and* J. Giboudeau, PhD

645 **Topical flurbiprofen decreases burn wound-induced hypermetabolism and systemic lipid peroxidation**
Cheryl LaLonde, BS, James Knox, MD, Ramona Daryani, BS, Deguang Zhu, MD, Robert H. Demling, MD, *and* Michaela Neumann, MD

652 **A comparison of polypropylene mesh and expanded polytetrafluroethylene patch for the repair of contaminated abdominal wall defects—An experimental study**
N. W. Law, MS, FRCS, *and* H. Ellis, CBE, DM, MCh, FRCS

656 **Long-term cholesterol feeding stimulates increased bile phospholipids and gallbladder prostanoid synthesis**
Stuart I. Myers, MD, Diane Haley-Russell, PhD, Lori Bartula, BS, *and* Wojtek Nabzdyk

663 **A comparison of portal versus systemic venous drainage in the pig small-bowel allograft recipient**
Hironori Kaneko, MD, Michael A. Fischman, MD, Thomas M. Buckley, MD, *and* Robert T. Schweizer, MD

BRIEF CLINICAL REPORTS

671 **Pathologic and hemodynamic sequelae of unilobar biliary obstruction and associated liver atrophy**
Nicholas S. Hadjis, MD, FRCS, J. Ian Blenkharn, MSc, Gregory Hatzis, MD, Charlene Demianiuk, RT, Muna Guzail, MD, *and* Irving S. Benjamin, MD, FRCS

677 **Pheochromocytoma of the urinary bladder**
Philip M. Sweetser, MD, Dana A. Ohl, MD, *and* Norman W. Thompson, MD

LETTERS TO THE EDITORS

682 **Management of biliary disease in patients with high risk cardiac disease**
A. Darzi, MB, P. Murchan, MB, *and* F. B. V. Keane, MD, FRCSI

682 **Reply**
Richard A Prinz, MD

683 **ES in patients with periampullary diverticula and gallbladder in situ**
Ivan E. Farkas, MD

This is a partial listing of May 1991 SURGERY contents

MAY 1991/VOLUME 161/NUMBER 5

The American Journal of Surgery

OFFICIAL PUBLICATION OF:

The Society for Surgery of the Alimentary Tract
The North Pacific Surgical Association
The Society for Clinical Vascular Surgery
The Society of Head and Neck Surgeons
The Southwestern Surgical Congress
The Association for Surgical Education

Contents

Papers of the North Pacific Surgical Association

PRESIDENTIAL ADDRESS

542 **History of the North Pacific Surgical Association**
Philip C. Jolly

SCIENTIFIC PAPERS

545 **Injuries to the Portal Triad**
David L. Dawson, Kaj H. Johansen, and Gregory J. Jurkovich

552 **Duplex Scanning for Arterial Trauma**
Mark Meissner, Marla Paun, and Kaj Johansen

556 **Anterior Sternal Retraction for Reoperative Median Sternotomy**
A. Craig Eddy, Donald Miller, Douglas Johnson, David Gartman, Mary Gregg, Margaret Allen, and Edward D. Verrier

560 **Use of Purified Streptokinase in Empyema and Hemothorax**
Ralph W. Aye, Daniel P. Froese, and Lucius D. Hill

563 **Early Experience with Mitral Valve Reconstruction for Mitral Insufficiency**
Albert H. Krause, J. Edward Okies, John C. Bigelow, U. Scott Page, Mark T. Metzdorff, Neal W. Salomon, and Ronald W. Schutz

567 **Clinical Parameters Predictive of Malignancy of Thyroid Follicular Neoplasms**
Noelle L. Davis, Marla Gordon, Eva Germann, R. Edward Robins, and Gregor I. McGregor

570 **Role of Surgery in Multimodality Therapy for Gastrointestinal Lymphoma**
Vicki L. Rackner, Richard C. Thirlby, and John A. Ryan, Jr.

576 **Efficient Management of Adrenal Tumors**
Richard J. Schwarz and Nis Schmidt

580 **Expression of Her-2/Neu Oncogene Protein Product and Epidermal Growth Factor Receptors in Surgical Specimens of Human Breast Cancers**
Roger E. Moe, Kris S. Moe, Peggy Porter, Allen M. Gown, Georgiana Ellis, and David Tapper

584 **Wound Complications After Modified Radical Mastectomy Compared with Tylectomy with Axillary Lymph Node Dissection**
Adele L. Vinton, L. William Traverso, and Philip C. Jolly

589 **Increased Incidence of Nosocomial Pneumonia in Mechanically Ventilated Patients with Subclinical Aspiration**
Gary W. Kingston, P. Terry Phang, and Mary J. Leathley

593 **Surgical Versus Percutaneous Drainage of Intra-Abdominal Abscesses**
Alan Hemming, Noelle L. Davis, and R. Edward Robins

596 **Inguinal Hernia Repair in Early Infancy**
R. Lawrence Moss and Edwin I. Hatch, Jr.

600 **Invasive Treatment of Pancreatic Fluid Collections with Surgical and Nonsurgical Methods**
Mark J. Szentes, L. William Traverso, Richard A. Kozarek, and Patrick C. Freeny

606 **Initial Two-Year Results of the Oregon Liver Transplantation Program**
C. Wright Pinson, Richard R. Lopez, Kent G. Benner, Emmet B. Keeffe, Michael K. Porayko, Anna W. Sasaki, Debora K. Bowers, Leslie J. Wheeler, Randall G. Lee, Roderick S. Johnson, Joyce A. Campbell, Scott H. Goodnight, Richard R. Davis, and Clifford W. Deveney

612 **Variation in Management Based on Type of Choledochal Cyst**
Richard R. Lopez, C. Wright Pinson, John R. Campbell, Marvin Harrison, and Ronald M. Katon

616 **Carotid Endarterectomy in a Community Hospital: A Change in Physicians' Practice Patterns**
James W. Asaph, Kenneth Janoff, Kim Wayson, Laura Kilberg, and Michelle Graham

619 **Role of Arteriography in the Preoperative Evaluation of Carotid Artery Disease**
David L. Dawson, R. Eugene Zierler, and Ted R. Kohler

A14 **Society Meetings**
A14 **Announcements**
A16 **Information for Authors**
A17 **Classified Advertising**
A18 **Classified Advertising**
A20 **Classified Advertising**
A19 ***The British Journal of Surgery* Table of Contents (vol. 78, no. 4, April 1991)**

Leading article

Br. J. Surg. 1991, Vol. 78, July, 769–770

Intra-arterial chemotherapy for breast cancer

Intra-arterial chemotherapy (IACT) is one form of regional chemotherapy. The basic concept behind giving drugs regionally is to increase the concentration locally and, perhaps, reduce the amount reaching the systemic circulation, thus widening the theraputic index. Klopp was the first person to draw attention to a differential effect after an accidental injection of nitrogen mustard into the brachial artery[1]: he observed that the affected hand was red and desquamated, unlike its partner. Whilst few new chemotheraputic agents have been released in the last two decades a greater understanding of the use of currently available drugs, allied to new materials and delivery techniques, has led to a reappraisal of this form of treatment.

IACT has been used in the management of head and neck cancers (by carotid infusion), limb sarcoma, limb melanoma, liver metastases, gastric and pancreatic cancer, recurrent pelvic tumours and breast cancers. It may be combined with hyperthermia, by using either external radiofrequency induction loops, or by passing blood through a heating unit prior to perfusion, or it may be coupled with filtration of the venous outflow to achieve yet higher tumour doses with lessened systemic toxicity.

The advantage of IACT over the conventional systemic route is related to total body clearance of a given drug, its extraction fraction and blood flow. Clearances are immutable and are tabulated in phamacology texts (there is no point in using a prodrug by this route – cyclophosphamide, for instance, needs activation by liver passage). The extraction fraction has a time dependent variable and the blood flow is manipulable by venous outflow blockade, a tourniquet or the use of microspheres.

A forthcoming article will describe the results from a series of patients with breast cancer treated with IACT. The method was first reported in the 1960s by Helman in South Africa[2] who used the thyrocervical trunk to approach the internal mammary artery and infused methotrexate before radiotherapy. The technique did not, however, gain popularity and lapsed until the studies of Stephens[3], Aigner[4], de Dycker[5] and Nogucchi[6] in the late 1980s. IACT may be used in three areas – as induction therapy for locally advanced disease, as treatment for end-stage chest wall (recurrent) disease, or as neoadjuvant treatment for disease that is traditionally primarily treated by surgery. Excellent response rates are seen if the patient has not been heavily pretreated, with many advanced lesions being rendered operable and some primary lesions disappearing completely. Worthwhile disease control, and some complete responses, are also seen with recurrent chest wall disease, although previous radiotherapy reduces the blood flow and means lower drug concentrations reach the involved area. Combinations of mitomycin-C, adriamycin and 5-fluorouracil (with leucovorin), or mitomycin-C, mitozantrone and methotrexate, administered at intervals, are the most commonly used regimens, though the use of single agents such as adriamycin or mitozantrone have been reported. The drugs are infused into either the subclavian artery, with a tourniquet around the upper arm, or directly into the internal mammary artery. Catheters may be placed percutaneously under radiological control (usually via the femoral artery in which case they are removed between courses) or by operation. The operative approach may be via the axilla or through a sub- or supra-clavicular incision. The catheter is either placed end-to-side into the wall of the artery (in which case manipulation of the position is impossible) or fed proximally through a purse-string suture in the arterial wall. It may be positioned under radiological screening; an infusion of blue dye allows confirmation that the tumour is perfused. Interestingly, if only part of the tumour is perfused then it is that area alone which responds; the non-perfused area (i.e. that getting the systemic dose) fails to respond. Repositioning of the catheter and subsequent chemotherapy may be used to treat such non-responding areas. The bulk of the agents used eventually reach the systemic circulation if not filtered, and so a systemic effect is seen. Alopecia may occur and haematological monitoring for toxicity is required. The median duration of response appears to be longer after this treatment than after other forms of primary therapy, although this has yet to be addresed in a trial.

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Where do we go from here given that the technique is feasible and works in cases resistant to other forms of treatment? The time has come for a multicentre trial comparing the response rate of IACT against that achievable by the intravenous route. The group which will be best evaluated will contain patients with large primary tumours who have had no prior treatment. Bonnadonna and colleagues[7] have shown that large cancers can be downstaged by intravenous chemotherapy, with quadrantectomy being performed rather than mastectomy. The group with recurrent chest wall disease is probably too heterogeneous to study meaningfully (and intravenous chemotherapy will often already have been tried) and the group with early disease should probably still be treated with standard therapy. If such a trial is to go ahead, clear definitions of what constitutes a response will be needed. We have found mammography to correlate poorly with histological response and the time of resection following completion of IACT has a bearing on the degree of histological effect seen. Histology is currently assessed on the Shimasato scale[8] which is imprecise; dynamic assessments of cell viability may be needed.

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Br. J. Surg. 1991, Vol. 78, July,
773–778

Improving survival in gastric cancer: review of operative mortality in English language publications from 1970

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In this review of English language publications from 1970, operative mortality following surgery for gastric cancer has been analysed. Operative mortality has declined in series reporting operations in successive decades to 1970, 1980 and 1990. Series reporting patients having surgery for gastric cancer in the decade to 1990 show a mean operative mortality rate of 7·8 per cent (median 4·6 per cent). This improvement may have contributed to the declining mortality rates for gastric cancer in the face of unchanging surgical workload. Results of operations for gastric cancer should be reported in a standard manner.

Many clinicians continue to view the results of gastric cancer surgery with pessimism. Although surgical resection offers the only prospect of cure, the operative mortality is regarded as unacceptably high by many practitioners. This view may cause physicians to advise against operations for gastric cancer, and may discourage them from referring patients with gastric cancer for surgical treatment. It may also lead some surgeons to believe that a high operative mortality is acceptable because it is the norm.

Throughout the world mortality from gastric cancer has been falling[1,2]. This has been interpreted as evidence that the disease is disappearing. We have, however, previously shown that in Scotland there has been no significant decrease in incidence in the past decade[3]. In this survey we examined the hypothesis that the observed reduction in mortality might be the result of better surgical treatment. Improved mortality in the face of unchanging incidence might be explained by improved operative mortality, or by more curative surgery or both.

At the Western General Hospital, Edinburgh, the operative mortality rate following gastric cancer resections fell from 13·2 per cent between 1975 and 1985 to 1·8 per cent between 1986 and 1989. We therefore reviewed the English language literature from 1970 to ascertain whether there was a similar trend in improvement of operative mortality in published series.

Materials and methods

All English language publications from 1970 listing operations for gastric cancer and operative mortality from Medline, Excerpta Medica (which began in 1974) and the Bibliography on Stomach Cancer (based on Medlars and searched by the Japan Information Centre of Science and Technology) were reviewed Case reports, reviews and abstracts were excluded Where operative mortality was satisfactorily documented this was recorded and the definition of operative mortality (e.g. 30 day, 3 month, in-hospital) was noted The series were divided into those in which patients had been operated on before 1960, 1970, 1980 and before 1990.

Of the 207 papers reviewed, 57 were excluded as they did not document an operated series, did not record operative mortality, involved selected patient groups (e g. atomic bomb survivors), included less than ten patients or included adjuvant therapy A further 39 were excluded as they contained material which had already been included from another paper and seven could not be traced in original form. One major European study[4] was excluded because the years of study were not specified The remaining 103 papers from 24 countries were included in the study.

Results

In only one study[5] had patients been operated on exclusively before 1960, and the 3-month operative mortality rate in this series was 25 per cent The remaining 102 series have been analysed.

There were 18 studies in which the patients had been operated on before 1970 (*Table 1*). In only five of these[6–10] was the operative mortality rate below 10 per cent. In seven series it lay between 10 and 20 per cent[11–17] and in the remaining six was >20 per cent[18–23] The median value was 14·9 per cent and the mean was 16·2 per cent (s e 2·2; 95 per cent confidence limits 11·6, 20·8)

Series showing patients operated on before 1980 are shown in *Table 2*. Of the 36 series in this group, in 12 the operative mortality rate was <10 per cent[8,24–34] In 19 it lay between 10 and 20 per cent[35–53] and in only five was it >20 per cent[54–58]. The median value was 13 per cent and the mean was 12·3 per cent.

Of the 49 series with patients operated on before 1990 (*Table 3*), 33 had an operative mortality rate of <10 per cent[59–90]. Fourteen had an operative mortality rate of between 10 and 20 per cent[63,91–103] and only two had an operative mortality of >20 per cent[104,105]. The median was 4·6 per cent and the mean was 7·8 per cent (s.e. 1·0, 95 per cent confidence limits 5·8, 9·9).

At least 11 centres have reported a decline in operative mortality with time. These are listed in *Table 4*. One UK series[73], the largest so far reported, has failed to show a decrease in operative mortality in successive quinquennia between 1957 and 1981. A series from the USA[35] reported no change in mortality between 1956 and 1965, and 1966 and 1975

Discussion

A study of this nature has several problems to overcome. Many series include not only curative and palliative resections but also palliative bypass and laparotomy alone Furthermore, most of the series reviewed contained a mix of distal gastrectomy, total gastrectomy and oesophagogastrectomy, each of which carries different degrees of operative risk[4,104]. Similarly, operations for early gastric cancer are generally of lower risk and where a series has analysed only early gastric cancer this has been noted in the Tables.

A further difficulty when comparing series is that there is

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Table 1 *Operative mortality in patients with gastric cancer undergoing operation in series closing before 1970*

Operative mortality	First author	Country	n	Operative mortality (%)	Years studied	Comments
<10%	Yamada[10]	Japan	195	0	1965–1970	30 day. Early gastric cancer only
	Nagata[8]	Japan	292	2·4	1965–1969	30 day
	Cady[6]	USA	403	6·4	1957–1966	Not defined
	White[9]	USA	242	7·1	1953–1966	30 day
	Mine[7]	Japan	438	8·8	1955–1963	30 day
10–20%	Zacho[17]	Denmark	776	11·3	1959–1969	Not defined. Radical procedures
	Nielson[15]	Denmark	385	14·0	1955–1964	Not defined
	Svennevig[16]	Norway	220	14·8	1959–1968	30 day
	Bucholtz[11]	USA	206	14·9	1962–1966	In-hospital
	Cassell[12]	UK	854	15·7	1948–1962	In-hospital
	McNeer[14]	USA	94	17·0	1950–1964	In-hospital. Total gastrectomy
	Inberg[13]	Finland	976	18·3	1956–1965	30 day Total or proximal gastrectomy
>21%	Lundh[22]	Europe multicentre	901	23·0	1966–1968	30 day
	Moore[23]	Canada	1030	23·5	1941–1970	Not defined. Proximal subtotal resections
	Desmond[20]	UK	1168	25·0	1944–1970	Not defined
	Henrichson[21]	Denmark	49	26·5	1949–1971	30 day
	Costello[19]	UK	226	31·0	1960–1969	3 month. Radical operations only
	Lulu[18]	USA	100	31·4	1954–1970	30 day

no universally accepted definition of operative mortality. The definitions encountered included '30 day', 'in-hospital', 'as a direct result of the operation' and '3 month'. The widely respected General Rules for Gastric Cancer Study in Surgery and Pathology published by the Japanese Research Society for Gastric Cancer[106] recommends that the definition should be death within 30 days of operation. Those who have analysed the problem with respect to colorectal cancer have made the same recommendation[107].

The analysis of these series shows a distinct trend towards lower operative mortality. In the era of patients operated on before 1970, only five of the 18 series reporting operative mortality gave an operative mortality rate below 10 per cent. For patients operated on before 1990 on the other hand 33 of the 49 series recorded an operative mortality rate of <10 per cent

In the pre-1970 era two series recording an operative mortality rate of <10 per cent[6,9] were from the USA. One[9] was a selected series of patients who were operated on for cure, the majority (73 per cent) by a distal gastrectomy. Analysis of subgroups in this series shows operative mortality rates of 13 per cent for oesophagogastrectomy and 18 per cent for total gastrectomy. The three others in this era were from Japan[7,8,10], one of which was concerned only with early gastric cancer.

Whereas six of the pre-1970 series have an operative mortality rate of >20 per cent, there were only two series in the pre-1990 group with this mortality rate. A Swedish report[105] had a 28 per cent in-hospital mortality rate in a series of 141 patients operated on for cure between 1972 and 1982. The largest European series yet reported from the West Midlands region, UK[104], had a 30-day operative mortality rate of 26·9 per cent for patients operated on between 1957 and 1981 The majority of patients in this series were operated on before 1970 and the series is therefore more representative of the earlier era. Moreover it demonstrates marked differences in operative mortality rates among the 159 surgeons involved, reiterating the observation that operative series involving many surgeons usually report poorer results. Of the seven series in the pre-1990 era which report an operative mortality rate of zero, three are from the USA[61,63,77], two are from Japan[69,80], one is from South Africa[66], and one from Australia[59]. Four of the non-Japanese series are exclusively cases of early gastric cancer. The Spanish series[82] with a 1·4 per cent mortality rate is also composed exclusively of patients with early gastric cancer.

The difference between the survival rates reported from Japan and those from the rest of the world has been so great that it has led to the suggestion that the biology and natural history of the disease in Japan is somehow different. Similarly, the lower Japanese operative mortality rates have been variously attributed to a higher proportion of patients with early disease, younger mean age of Japanese series (the mean age is some 10 years younger in Japan than in the West), lower incidence in Japan of coronary artery, cerebrovascular and chronic obstructive airways disease, and a body habitus in Japanese patients which makes surgery technically easier. However, if the Japanese series are excluded from the decades to 1980 and 1990 a decline is still evident. The mean operative mortality rate for the decade to 1990 is 9·3 per cent and the median is 9·6 per cent compared with a mean of 13·1 per cent and median of 13·4 per cent for the previous decade.

Eleven of the 13 centres which have reported trends in operative mortality have shown a decline over successive study periods. In the UK, the Glasgow series[41] shows a decline in operative mortality rate from 17·6 per cent for patients operated on between 1974 and 1979 to 8·4 per cent between 1980 and 1984. That from Edinburgh[91] shows a decline from 15·3 per cent for operations between 1975 and 1985 to 1·8 per cent for resections between 1986 and 1989. Similar results have been reported from Norway[89], Denmark[17], Germany[92], Italy[38], Morocco[96] and of course from Japan[8,72].

It is the Japanese above all who have produced evidence to show that the results of gastric cancer treatment can be improved. A combination of screening for early disease, describing the endoscopic features of early gastric cancer, and introducing the R2/R3 radical resection based on meticulous study of gastric lymphatic drainage have combined to demonstrate that impressive cure rates can be attained. One important feature of Japanese work in this area has been the methodical recording of results in a standard manner using agreed definitions, conventions and nomenclature.

Our ability to improve standards elsewhere in the world would be enhanced if authors reported results in a standard

Table 2 *Operative mortality in patients with gastric cancer undergoing operation in series closing before 1980*

Operative mortality	First author	Country	*n*	Operative mortality (%)	Years studied	Comments
<10%	Nagata[8]	Japan	299	0·7	1975–1979	30 day
	Rheault[30]	Canada	64	1·7	1948–1978	Not defined. Early gastric cancer only
	Yamada[33]	Japan	1952	2·4	1965–1977	30 day
	Imanaga[28]	Japan	1628	2·8	1964–1973	30 day
	Yap[34]	Philippines	465	2·8	1950–1974	30 day
	Salo[31]	Finland	438	5·0	1975–1980	In-hospital
	Houghton[27]	UK	35	5·7	1965–1974	Immediate postoperative deaths. Early gastric cancer only
	Suehiro[32]	Japan	377	3·9	1970–1980	30 day
	Diehl[25]	USA	164	6·0	1970–1980	Not defined
	Armstrong[24]	S. Africa	201	6·8	1974–1975	In-hospital
	Gebhardt[26]	W. Germany	130	8·0	1970–1979	Not defined
	Lygidakis[29]	UK	118	9·7	1964–1980	'Due to operation'
10–20%	Stark[52]	USA	66	10·0	1970–1979	30 day
	Choi[40]	Hong Kong	119	10·0	1974–1979	Not defined
	Hoerr[43]	USA	478	10·2	1950–1972	In-hospital
	Inberg[45]	Finland	2590	10·5	1946–1972	30 day
	Bozzetti[38]	Italy	61	11·5	1965–1980	Palliative resection only
	Hughes[44]	Australia	220	13·0	1950–1973	Not defined
	Adashek[35]	USA	501	13·0	1956–1975	Not defined
	Papachristou[49]	USA	143	13·3	1955–1975	Caused by the disease
	Inberg[46]	Finland	305	13·4	1956–1977	30 day
	Bizer[37]	USA	171	13·7	1972–1976	Not defined
	Beradi[36]	USA	41	14·6	1963–1971	30 day
	Schrock[51]	USA	120	15·0	1940–1975	In-hospital
	Longmire[47]	USA	501	15·0	1956–1975	Not defined
	Bozzetti[39]	Italy	143	15·4	1965–1980	In-hospital
	Viste[53]	Norway	206	15·5	1976–1980	30 day
	Oohara[48]	Japan	406	16·5	1959–1980	In-hospital Patients >70 years only
	Faivre[42]	France	217	17·6	1976–1980	30 day. Curative resection
	Cunningham[41]	UK	328	17·6	1974–1984	30 day
	Paolini[50]	Italy	110	18·0	1971–1978	Total gastrectomy
>21%	Nelson[57]	Australia	229	20·9	1970–1975	Not defined
	Shiu[58]	USA	213	21·0	1955–1975	Due to operation
	Ekbom[56]	USA	144	22·2	1957–1978	Not defined
	Battezat[54]	Italy	422	24·2	1965–1979	30 day
	Dupont[55]	USA	1497	26·5	1948–1973	30 day

manner. Reports of operative series of gastric cancer should define operative mortality as either '30 day' or 'in-hospital'. A mortality rate should be defined for all patients undergoing surgery and separate rates recorded for those patients having curative resection, palliative resection, bypass and laparotomy alone. Separate rates should be recorded for distal gastrectomy, total gastrectomy and thoracoabdominal oesophagogastrectomy. Reports should also contain analysis of tumour stage using the Union International Contra le Cancrum (UICC) classification.

We have previously shown that, in Scotland, mortality rates have fallen significantly over the past decade while incidence has not fallen significantly[3]. This may in part be explained by improving surgical treatment. Advances in diagnostic techniques have resulted in earlier diagnosis not only in Japan, but now in the UK[108]. Improving perioperative care, however, must be regarded as the major contributor. The present study has demonstrated that in series published over the past 20 years surgical mortality rates have progressively fallen and in the majority of series of operations performed in the decade to 1990 the operative mortality rate is under 10 per cent. This knowledge should encourage clinicians to refer patients for surgical treatment for gastric cancer.

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Table 3 *Operative mortality in patients with gastric cancer undergoing operation in series closing before 1990*

Operative mortality	First author	Country	*n*	Operative mortality (%)	Years studied	Comments
<10%	Mori[80]	Japan	23	0	1965–1982	30 day
	Carter[63]	USA	31	0	1974–1982	30 day. Early gastric cancer only
	Brando[61]	USA	23	0	1970–1986	30 day
	Longo[77]	USA	17	0	1972–1985	Early gastric cancer only
	Furukawa[69]	Japan	60	0	1980–1986	30 day
	Dent[66]	S. Africa	43	0	1982–1986	30 day
	Beach[59]	Australia	20	0	1982–1987	Early gastric cancer only
	Ellis[67]	USA	144	0·8	1970–1988	30 day. Oesophagogastrectomy for carcinoma of cardia
	Habu[72]	Japan	338	0·9	1980–1984	30 day
	Soga[85]	Japan	274	1·1	1981–1985	30 day
	Oleagoitia[82]	Spain	142	1·4	1975–1985	30 day Early gastric cancer only
	de Aretxabala[65]	Japan	300	1·7	1973–1983	30 day
	Ti[87]	Singapore	69	1·9	1979–1984	In-hospital
	Nakajima[81]	Japan	8000	1·9	1946–1986	Direct surgical deaths
	Lin Chao-Hong[75]	China	1399	2·1	1960–1982	30 day
	Gouzi[70]	France	169	2·4	1980–1985	Not defined
	Moreaux[79]	France	114	2·6	1964–1985	30 day. Carcinoma of cardia
	Cady[62]	USA	176	2·8	1967–1982	In-hospital
	Fass[68]	Germany	102	3·0	1985–1988	Not defined
	Kawaura[74]	Japan	70	4·3	1972–1982	30 day
	Shiu[84]	USA	246	4·5	1960–1984	Postoperative complications
	Yan[90]	USA	196	4·6	1958–1982	Operation or complication
	Svartholm[86]	Sweden	72	5·5	1982–1986	30 day
	Boddie[60]	USA	219	5·6	1970–1981	Curative procedures only
	Valen[88]	Norway	1025	7·0	1982–1984	In-hospital
	Viste[89]	Norway	763	8·3	1982–1984	Not defined
	Cunningham[41]	UK	110	8·4	1980–1984	30 day
	Lindahl[76]	Norway	312	8·7	1974–1984	30 day
	Hartley[71]	Australia	322	8·9	1973–1981	In-hospital
	Miholic[78]	Austria	98	9·0	1980–1987	30 day
	Irvin[73]	UK	122	9·0	1979–1986	30 day
	Coluccia[64]	Italy	149	9·4	1976–1981	Not defined
	Saario[83]	Finland	52	9·6	1975–1982	In-hospital
10–20%	Msika[101]	France	156	10·0	1967–1984	Postoperative
	Hassler[95]	Switzerland	69	11·0	1973–1982	Not defined
	Diggory[94]	UK	27	11·0	1977–1984	30 day
	Meyers[100]	USA	255	11·0	1953–1983	30 day
	Carter[63]	USA	31	11·5	1974–1982	30 day
	Meyer[99]	W. Germany	1510	12·4	1968–1987	Not defined
	Bittner[92]	W Germany	186	13·4	1969–1984	Related to operation
	Keighley[98]	UK	136	14·5	1976–1983	Not defined
	Akoh[91]	UK	183	15·3	1975–1985	30 day
	de Calan[93]	France	91	16·0	1968–1983	'All postoperative deaths'
	McBride[97]	USA	2062	16·0	1944–1984	30 day
	Jain[96]	Morocco	94	17·0	1975–1986	Not defined
	Ponsioen[102]	Holland	66	18·2	1970–1983	30 day
	Scott[103]	USA	213	19·0	1960–1983	Not defined
>21%	Allum[104]	UK	31 567	26·9	1957–1981	30 day
	Sjostedt[105]	Sweden	141	28·0	1972–1982	In-hospital

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Table 4 *Operative mortality in patients with gastric cancer undergoing operation in series reporting a decline in mortality rate*

First author	Earlier operative mortality % (years)	Later operative mortality % (years)
Jain[96]	30·0 (1975–1980)	7·5 (1981–1986)
Viste[89]	15·5 (1976–1980)	8·3 (1982–1984)
Bittner[92]	13·4 (1969–1984)	5·0 (1979–1984)
Cunningham[41]	17·6 (1974–1979)	8·4 (1980–1984)
Akoh[91]	15·3 (1975–1985)	1·8 (1986–1989)
Zacho[17]	13·0 (1949–1958)	11·0 (1959–1969)
Nagata[8]	2·4 (1965–1969)	0·7 (1975–1979)
Habu[72]	3·1 (1976–1979)	0·9 (1980–1984)
Bozzetti[38]	28·0 (1965–1970)	8·0 (1976–1980)
Yan[90]	14·7 (1933–1957)	4·6 (1958–1982)
Cady[62]	6·0 (1957–1966)	2·8 (1967–1982)

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Statistical aspects of research methodology

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Many reports in the medical literature are flawed through poor presentation of numerical results, or, more seriously, by the use of inadequate or inappropriate statistical methodology. This article expands on the more complex methodological issues. The main emphasis is on discussing key aspects of experimental design, and the idea of reporting results in terms of confidence intervals rather than P *values.*

It is hardly original to point out that the standard of statistical thinking embodied in a substantial proportion of the medical literature is woefully inadequate More than 25 years ago Yates and Healy remarked that 'It is depressing to find how much good biological work is in danger of being wasted through incompetent and misleading analysis of numerical results'[1], and I am aware of over 150 articles which have been published since then reviewing the statistical standards of published medical papers. These reviews reveal a remarkable and depressing consistency, with typically around 50 per cent of reviewed papers being found to contain clear statistical errors My own informal review of papers from three consecutive issues of the *British Journal of Surgery* suggested that this journal is not immune to this common problem[2], and a recent editorial in the *American Journal of Surgery* suggests that a similar position holds on that side of the Atlantic[3]. As Yancey points out in that editorial, these errors are not trivial misunderstandings, but 'are of the magnitude of claiming that one surgical procedure is superior to another when no such valid scientific data are presented'.

In a set of statistical guidelines which accompany this article I have attempted to set out in detail some rules to help in avoiding the more straightforward problems of presenting data and the results of statistical analyses[4]. In this paper I shall explore some of the 'deeper' problems, problems which frequently lead to inappropriate conclusions being drawn. These remarks have more to do with research methodology than with the minutiae of presenting and analysing data, but I make no apologies for that. I see the statistician's role as being the auditor of the entire research process from the conception of a hypothesis through to the publication of a final report, with a responsibility of ensuring that the goal of achieving a scientifically and clinically relevant answer is attained in as timely and efficient a manner as is possible. To play such a full role does of course require that the statistician is involved from the outset, and so it is appropriate that I should begin with a discussion of the design of clinical studies, which will be followed by discussion of the more specific points of estimation as opposed to significance testing and multiple comparisons.

Design

Good research is characterized by studies which address well defined, prespecified questions. Having been involved in the design of a wide range of studies, I find a great unifying factor is how, having decided on the precise question being addressed, the study essentially designs itself! In the context of clinical trials, Schwarz and Lellouch have pointed out with enormous insight that there are essentially only two types of question and hence only two types of clinical studies, explanatory and pragmatic[5,6]. Explanatory studies look at mechanisms, and aim to advance knowledge by adhering to 'laboratory conditions'. Pragmatic studies look at outcome, and aim to give sound treatment recommendations by mimicking the realities of clinical medicine These two types of study are designed in very different ways, and I contend that the only crucial decision that needs to be made in the writing of a study protocol is the choice between an explanatory and a pragmatic approach In practice most studies attempt to answer both types of questions at once, but attempting this risks reaching an uneasy compromise, leading to a study which is incapable of providing valid answers to either type of question

To emphasize this distinction, and also to demonstrate how having decided whether a study is primarily explanatory or pragmatic, that the study designs itself, I shall run through a number of the points which have to be specified in the design of a clinical study. These points are the subjects to be entered; the treatments to be compared; the delivery of these treatments; outcome measures; the conduct of the study; the analysis of the results, and their interpretation.

Subjects

In an explanatory study, one adopts the attitude of a laboratory worker, striving to control all possible sources of extraneous variation. One must select as homogeneous a group of subjects as possible. Moreover, the subjects must be selected in such a way that they are likely to 'respond' to treatment. This essentially means triage: not so ill that the patients will do badly even with treatment, and not so fit that they will do well even without treatment By focusing on this responsive, homogeneous population, the required sample size is likely to be quite modest

On the other hand, the pragmatist needs to enrol all comers, that is, a representative sample from the target population which would eventually receive the trial therapy should the study yield a 'positive' result. One also might initiate treatment on the basis of a 'working' diagnosis rather than demanding a definitive diagnostic investigation. For example, in the context of aneurysmal subarachnoid haemorrhage, one might well initiate treatment on the basis of signs and symptoms, rather than demanding angiographic evidence of a ruptured aneurysm. The heterogeneity of the study population, together with the fact that some subjects will not even be suffering from the complaint that one is attempting to treat, means that a large sample size is required to detect (i.e. to achieve statistical significance) treatment effects which are of clinical significance.

Treatment/delivery

Clearly there are ethical constraints relating to the choice of a control treatment, but ideally in an explanatory study one would compare the new treatment with a placebo or a null intervention, whereas in a pragmatic study one compares a new

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intervention with 'standard best practice', which would normally involve an active control. In an explanatory trial, again to control extraneous variability, one wishes to use a rigid treatment protocol. Thus for example in an explanatory surgical trial it would be important to be confident that a patient's lesion was 'operable' before the patient was enrolled, so that the subjects are treated in a uniform manner with no exclusions or protocol deviations. This is less important for a pragmatic trial, where one is rather assessing a treatment 'package' or a strategy for managing a certain population of patients.

Outcome measures

In an explanatory study one is always striving to maximize sensitivity, and so one must choose an outcome measure that is sensitive and relates directly to the intervention under investigation. For example in assessing a reconstructive vascular procedure in claudicants, one might measure efficacy in terms of the ankle/arm pressure ratio. The pragmatist on the other hand looks at 'clinical' outcome, and few patients will be excited by having their ankle/arm ratio improved from 0·4 to 0·7! It would be more appropriate in a pragmatic study to assess, say, treadmill walking distance, or the rate of progression to amputation Once more the pragmatic study has to sacrifice sensitivity or efficiency in order to enhance the clinical relevance of the findings.

Conduct

As with the previous issues, the explanatory study is conducted under carefully controlled and monitored 'laboratory' conditions, with exhaustive data recording. In contrast, the pragmatic study mimicks real life, and data recording is reduced to a minimum. What is imperative however is that there is meticulous follow-up of the patients, for the pragmatic study looks at the entire population of enrolled patients.

Analysis

In spite of the investigator's best efforts, there is always a risk of protocol violations. In an explanatory study, such individuals would be excluded from the analysis, and if there was a large number of such exclusions then the study would be seriously compromised. With a pragmatic study the analysis is based on the 'intention-to-treat' principle, that is, one analyses all randomized subjects, irrespective of whether they received their allocated treatment. Many clinicians find this approach counter-intuitive, but it is justified by the fact that one is assessing a management strategy rather than a rigidly defined intervention, and it is the 'intention-to-treat' analysis that actually has the greatest clinical relevance

Interpretation

The contrast between the two approaches emerges finally in the fundamentally different conclusions which may be drawn Explanatory studies look at mechanisms and *potential* benefits. It is dangerous to base treatment decisions on such evidence. What is needed rather for treatment decisions is a pragmatic study which assesses whether the potential benefits can be realized in practice.

In the above discussion I have of course painted a black and white picture of a rather grey area. Many studies try to reach a compromise between the two extreme approaches, but I believe that there is no secure middle ground. Rather study design must lean towards one of the two extremes, with the choice being determined by where the intervention under investigation is along its development path. Logically the explanatory study must come first, using modest resources to demonstrate a potential benefit, to be followed by a much larger but simpler pragmatic study which assesses whether the potential can be realized in clinical pactice.

Sample size

A key practical point in study design is the choice of sample size. In general terms, explanatory studies need only recruit a small number of subjects whereas pragmatic studies require very large numbers. This can be made more specific by performing what is known as a power calculation. The power of a statistical comparison is the probability (chance) of the study being positive (i.e achieving statistical significance at a specified level) should a postulated treatment effect actually hold. The sample size must be large enough so that one can be relatively confident of not missing a clinically important difference (should such a difference exist), and equally, so that a negative finding excludes the possibility of a clinically important effect

Estimating the required sample size involves answering a series of questions. First, what is the main aim of the trial, and hence what is the primary outcome measure? In an explanatory trial this is likely to be a continuous measure, such as tumour mass or ankle/arm pressure ratio, whereas in a pragmatic trial it is more likely to be a discrete variable, such as dead or alive at 1 year, or controlled *versus* not controlled.

Second, what is expected to happen in the control group? For a continuous variable, an estimate of the mean and standard deviation is required, which might come from the literature or from a pilot study. For a discrete variable, an estimate of the 'event rate' is required.

Third, how small a difference is it important to be able to detect? This difficult question is a clinical one rather than a statistical one, as it comes down to asking what is a clinically significant difference. It is tempting to be optimistic and to say what one hopes to see with the new treatment. It is important rather to be realistic, and to ask how small a difference is one prepared to miss, should it actually exist.

Fourth, with what degree of certainty does one wish to detect such a difference, should it indeed exist? This probability of detecting a specified difference at a specified significance level is known as the power of a study. There is no universally accepted value at which one should aim, but a value in the range 80 per cent to 90 per cent is often regarded as being appropriate.

Given the answers to these questions, it is possible to calculate the required sample size using methods described in any standard textbook on clinical trials. As described above, explanatory trials, with their emphasis on efficiency, need quite modest samples sizes, in contrast to pragmatic studies where the result of the power calculations can be frightening! For example, to compare the effects of two drugs on blood pressure in mild hypertensives it would be sufficient to study a total of 200 patients over a few weeks. To compare the effects of the same drugs in the same low risk population in terms of the incidence of strokes would require many thousands of patients to be followed over several years.

Power calculations in the end can only give a rough guideline In practice, the sample size employed will be a compromise between statistical power and the resources available in terms of subjects, funds and time. However, it is foolish to embark upon a clinical investigation without the reassurance that there is a high probability of obtaining valid and clinically relevant results. Moreover, a detailed description of a power calculation in the published report of a clinical study is a very reliable indicator of a well conducted piece of research

Significance testing

Significance testing, the dark art of attaching a P value to a set of experimental data, is based on rather subtle arguments, and a very high proportion of statistical flaws in the medical literature stem from fundamental misunderstandings of the strengths and limitations of the procedure When one delves into the underlying logic, it rapidly becomes clear why misunderstandings arise. The logical structure of a significance test is an extension of a technique that is widely used in mathematics, namely proof by contradiction. If one wishes to prove that a statement is true, one begins by assuming rather that it is false. Starting from that premise, one follows a logical argument until a contradiction is reached. Reaching a contradiction by following a logical argument can only have one explanation, namely that one has started from a false premise. Thus the premise that the statement is false has been disproved, or in other words the truth of the statement has been established.

A significance test is simply a more complex version of this procedure, where instead of reaching a contradiction one observes an event which, given the starting premise, has an extremely low probability, which throws doubt on the premise rather than disproving it.

For example suppose that one was investigating the relative efficacy of two agents which were used in the prophylaxis of deep vein thrombosis (DVT). One's aim would be to demonstrate a difference in efficacy and so one begins by assuming the opposite, namely that there is no difference in efficacy, and one then attempts to knock down this 'null hypothesis'. This is done by collecting experimental data, which in this context might come from a randomized clinical trial. Suppose for the sake of argument that a total of 1000 patients were allocated at random so that 500 patients received each of the two experimental treatments, and suppose that in these groups there were observed respectively 30 and 50 DVTs Such a discrepancy could have arisen by chance, but this seems rather unlikely. All that the significance test does is to quantify the uncertainty. The *P* value is no more nor less than the probability (or chance) of observing a difference as marked, or even more marked, than that actually observed, under the null hypothesis that the treatments are in fact equally effective. In our example, using a χ^2 test, one finds that the *P* value is 0·02. This probability is so small that it throws doubt on the null hypothesis Chance is still a possible explanation of the observed difference, but the discrepancy is unlikely to have arisen under such circumstances, and one is tempted to seek a better explanation, namely that the null hypothesis is false, and that there is indeed a difference in relative efficacy.

By an arbitrary but very firmly established convention one takes 0 05 as the threshold to define the probability of an event being so low that one rejects the null hypothesis and claims to have established that a difference exists One has achieved 'statistical significance'. This is effectively defining a false positive rate, and by using the threshold of 0·05 one is saying that in a long sequence of significance tests, where no true difference exists, one is prepared wrongly to claim to have established a difference one time in 20 (i.e. in 5 per cent of the tests).

A number of points flow from this discussion. First, the *P* value is a measure of the strength of evidence against the null hypothesis, and is not the probability of the null hypothesis being true. (Indeed many would argue that it is not even sensible to talk about the probability of a hypothesis being true – statements are either true or false – but to pursue this requires one to delve deeper into the philosophical basis of probability than is appropriate at this point.) Second, the conventional threshold of 0·05 for a *P* value is very artificial, and there is little difference in the strength of evidence against the null hypothesis between $P=0·049$ and $P=0·051$. Third, if one obtains a 'non-significant' result then one has failed to demonstrate a difference, which does not mean that one has established equivalence A non-significant finding rather is analogous to the Scottish legal verdict of 'not proven', which is generally if mischievously regarded as meaning 'not guilty, but don't do it again'. In other words, a non-significant finding often simply reflects a lack of evidence, rather than a lack of difference. Fourth, seen in isolation, the *P* value has no clinical relevance, and so it should not be used (as it often is in abstracts) as if it were a descriptive statistic. It is a measure of the strength of evidence against the null hypothesis, and so depends on both the sample size (the larger the sample size the stronger the evidence) and on the magnitude of the difference (the larger the magnitude of the difference, the more extreme will be the *P* value).

Estimation

The final point in the above discussion brings out the fundamental weakness of the hypothesis testing approach, namely that statistical significance and clinical significance frequently do not go together. It is because of this limitation that there has been considerable recent encouragement in the medical literature to move away from significance testing and to use confidence intervals instead[7–9], with the idea being that rather than quoting an almost uninterpretable *P* value, one quotes an estimated treatment effect along with a measure of the precision of that estimate. For example in the hypothetical example quoted above the incidence of DVT in the two treatment groups was 6 per cent and 10 per cent respectively. Thus our estimate of the difference between the two incidences is 4 per cent Unlike the *P* value, this figure has an immediate clinical interpretation. If we use the first rather than the second prophylactic agent, then we can expect on average to prevent four DVTs for every 100 patients we treat. This figure of 4 per cent is only an estimate, and the corresponding confidence interval tells us how reliable is the estimate The 95 per cent confidence interval for the difference is 1–7 per cent, and so although 4 per cent is our best estimate of the treatment difference, the data are in fact consistent with any value from 1 per cent to 7 per cent. Indeed, with the (conventional) choice of a 95 per cent confidence interval, there is still a 5 per cent chance that the interval has failed to 'capture' the true treatment difference. Notice that the 95 per cent confidence interval does not straddle the value zero, which tells us that the data are not consistent with no treatment difference, or in other words we have established a treatment difference. This finding ties in with our earlier finding of a 'significant' difference at the 5 per cent level, but we now know in addition the likely magnitude of this difference, which allows an assessment of its clinical significance

Multiple comparisons

A further problem which stems frequently from significance testing, and a problem that is not overcome by the use of confidence intervals, is that of multiple comparisons. As explained above, by using the conventional threshold of $P=0·05$ to define a 'significant' result, one is accepting a risk of one in 20 of obtaining a false positive result *every* time that one compares two groups which are in fact equivalent This can perhaps be accepted in the context of a single test of a prespecified hypothesis. However, it is very common for a single report to include implicitly or explicitly the results of a very large number of significance tests. Thus as one accepts more and more risks of one in 20, it becomes increasingly likely that some 'significant' but spurious finding will emerge

This multiple testing can arise in several different ways. It is common to use several different endpoints to assess the impact of a treatment, and, for example, in a surgical trial one might analyse blood loss, operating time, operative complications, postoperative complications, length of hospital stay, time to return to work and length of survival. Equally it is common to assess the same endpoint at different time points, where for example one might assess tumour mass at 1, 3 and 12 months after treatment: One might also include more than two experimental groups, which generates yet more comparisons. If, in spite of making a large number of such comparisons, one fails to achieve significance, then it is tempting to examine subgroups, with patients classified by age, sex, stage of disease, grade of tumour, etc. If this still fails to achieve significance, then it is common to treat the analysis as an interim analysis and to go back and recruit additional patients in a game of 'chase the *P* value'. All of these manoeuvres make a nonsense of significance testing, which is based on the foundation of a single test of a prespecified hypothesis, and yet they are rife in the medical literature.

There do exist statistical techniques to mitigate some of the problems associated with multiple comparisons, but before discussing these I shall set out three different strategic approaches to the area.

The first is simply to refuse to perform multiple comparisons. The most sensitive and scientifically sound studies address well defined questions, and so only a single statistical test should ever be required. This is a defensible if extreme view, but one which I believe to be fatally flawed through not recognizing the crucial role that serendipity has played throughout the history of medical research. Many fundamental breakthroughs stem from unexpected findings and a flash of inspiration rather than from statistical pedantry.

A second approach is not to impose any restriction on the number of tests to be performed, but to 'adjust' the P value so as to limit the overall risk of making *any* false positive statement to at most one in 20. There are many statistical techniques which support this approach, the simplest and most intuitive of which is the Bonferroni correction. Here one simply takes the individual P values and multiplies each by the number of tests performed. One then only claims 'significance' if the adjusted P value is less than 0·05. For example, if one is performing five tests, then one would need to achieve a P value of less than 0·01 before claiming significance at the 5 per cent level. One accepts a risk of one in 100 five times, limiting one's overall risk of making a false positive statement to less than one in 20.

This approach is both simple and safe, and it is particularly useful to apply when reading a paper where one suspects that a large number of comparisons have been made. If ten comparisons are reported (and who knows how many others were performed but not reported as they were 'negative'?), then one should not place very much weight on an isolated comparison which achieves, say, $P = 0{\cdot}008$ Such a finding could easily have arisen by chance.

However, while the approach is invaluable in restraining the over-enthusiastic claims of other workers, it is not in general a sound basis for research. What one is gaining by controlling the type I error one loses in sensitivity, since in effect one has to achieve a very extreme P value before one can even claim $P < 0{\cdot}05$.

A third approach, and the one which in general I would advocate, is to set down *a priori* a hierarchy of comparisons of interest. There should be a single comparison of primary interest, upon which the sample size (power) calculation would be based, and the analysis of which would be taken at face value. Thus one preserves sensitivity for the most important question, since one only has to achieve $P < 0{\cdot}05$ in order to be able to claim $P < 0{\cdot}05$. There would then be a limited number of prespecified secondary comparisons, which would carry a lesser weight, but which if significant after a Bonferroni correction (which would not be too severe, because of the limited number of comparisons) should not be too lightly dismissed. After that, any comparisons of interest would be made in a purely exploratory fashion, in an attempt to *generate* hypotheses for future studies. Even the most extreme of P values should be given very little weight if it emerges from a *post hoc* 'data dredge', until there is independent supporting evidence from other studies.

As well as these issues of strategy, there are also a number of technical issues. This is a very wide area, and indeed there are entire textbooks devoted to the topic of multiple comparisons, but I shall attempt to describe some techniques that are particularly valuable in medical research. The common theme underlying many of these techniques is that one aims to perform a single global test of a carefully specified hypothesis in place of, or in support of, a battery of similar tests.

Multiple treatment groups

In a study with three or more treatment groups, it is common practice to perform separate tests comparing every possible pair of treatments. With, for example, five groups, this generates ten pairwise comparisons, and a substantial risk of making at least one false positive statement. If there is no particular structure to the treatment groups, then the appropriate analysis is rather to perform a single overall test to see whether there is evidence of a difference between any of the groups. In a situation where with two groups one would have used a t test, the appropriate test is the one-way analysis of variance (ANOVA), and the non-parametric equivalent of this is the Kruskal–Wallis test. For discrete data, the χ^2 test can be used to compare any number of groups. If this overall test does give evidence of some difference, then one is justified in performing follow-up paired comparisons in an attempt to identify where the differences lie. If there is some structure to the study groups, with perhaps increasing doses of a drug or else a factorial structure, then more sensitive tests are available, and professional statistical advice should be sought.

Repeated measures

This is the name for the very common design where the same variable is measured repeatedly on the same subject. For example in a study of analgesia, a pain score might be recorded postoperatively every hour for 6 h. It is common practice to analyse such data by performing separate statistical comparisons at each time point. It is far more appropriate to summarize each individual's pain profile by a single number (perhaps an 'area under the curve' or the time until the score falls below a threshold) and to analyse these summary measures[10]. Again, if this does give evidence of a difference, then one is justified in looking at the time course in more detail to try to describe the difference.

Subgroups

This area probably generates more spurious and misleading conclusions in the medical literature than any other. It is depressingly common to find a 'negative' study where the authors divide the subjects into a large number of subgroups, perform separate statistical tests within each subgroup, and conclude that a 'significant' treatment benefit exists for, say, male patients aged over 65 with advanced disease and with a previous history of cardiovascular disease. This is then generally followed by a tortuous discussion pointing out how in retrospect it is obvious that this is precisely the subgroup which would be expected to benefit most.

This is nonsense for at least two reasons. First, one must realize that it is highly unlikely *a priori* that any study will provide strong evidence of a subgroup effect. Even studies which are well designed will have a sample size which is adequate only to address a primary comparison of all subjects Poorly designed studies do not even have an adequate sample size to do this. Thus one is very unlikely to have the power to detect a genuine treatment effect in a subgroup of patients. Second, with modern computer packages it is possible to examine literally millions of different subgroups, making it almost inevitable that some spurious 'significant' result will be obtained.

Accepting *a priori* that one almost certainly does not have an adequate sample size for such an analysis, the correct statistical approach is not to perform separate tests with subgroups of patients, but rather to test for 'interactions', that is evidence that treatment effects differ systematically between subgroups. Some of the tests are quite difficult to perform, and this is another area where professional statistical assistance should be sought. In general, one should be very wary of believing any claims for subgroup effects, unless they are supported by independent evidence and by compelling arguments concerning mechanisms.

Interim analysis

A final common way of generating large numbers of comparisons is by performing repeated analyses of the accumulating data from an ongoing study. Although by no means unique to surgery, surgical trialists appear in general to have a very casual approach to interim analysis. Indeed the very existence of important 'career' meetings where junior surgeons are encouraged to present the results of work in progress tends to bring about premature reporting in a way which would not even be contemplated for major drug trials in cardiovascular medicine, where interim results are only available to small expert monitoring committees whose members are sworn to secrecy.

As any trial progresses there will be random peaks and troughs, as the treatment difference fluctuates around a slowly emerging trend. If one follows the accumulating results too closely, then there is a risk (and a temptation!) of stopping the trial at the peak of a random 'blip' when the new treatment appears to be performing particularly well. Again there do exist statistical techniques to allow such accumulating data to be analysed in a valid way, either on a patient by patient basis, or on the more common 'group sequential' basis, where there is an analysis after, say, every 50 patients[11]. However, it is essential for the design to be set out in advance, and yet again this is an area where expert statistical assistance should be sought at an early stage.

Discussion

In this paper I have attempted to demonstrate that statistics is far more than a battery of tests and techniques, and is more of a philosophical approach to research. Many of the underlying ideas are certainly subtle, as is amply demonstrated by the frequency with which statistical methods are abused in the medical literature. However, I hope that I have also demonstrated how the current emphasis in medical statistics is to move away from unnecessary technicalities and to report results in a way that is clinically meaningful. If nothing else, I shall maybe have encouraged some practitioners to seek professional statistical support sooner rather than later.

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Paper accepted 20 January 1991

Surgery in the Third World

I am anxious to build up a list of surgeons in all specialties from the United Kingdom and Northern Ireland (active or recently retired consultant, or higher surgical trainee) who would like to spend time working and teaching in a third world country.

In most cases accommodation and subsistence is provided and in some air fares also. Periods abroad vary from one month upwards but 3–6 months are usually preferred.

Please write to me, care of the Overseas Doctors Training Scheme Office at the Royal College of Surgeons of England, 35–43 Lincoln's Inn Fields, London WC2A 3PN, UK

Sir Ian Todd KBE FRCS

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Statistical guidelines for The British Journal of Surgery

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A set of statistical guidelines is presented which should be followed by authors preparing manuscripts for submission to The British Journal of Surgery. *Simple points relating to presentation are explained in full, and more complex issues are highlighted and discussed in an accompanying review article.*

In 1988 I published a paper in *The British Journal of Surgery* which reviewed the standard of statistical presentation of articles in three consecutive issues of the *Journal*[1] The review was relatively critical, highlighting problems in the areas of study design, presentation of data, statistical analysis and interpretation. Since that time I have served as the statistical consultant to the *Journal*, refereeing a proportion but by no means all of the manuscripts submitted for publication. Many of the manuscripts received by the *Journal* still suffer from major statistical flaws[2], and a proportion of these flaws continue to evade the referees' and editors' scrutiny and appear in print.

Some of these problems are relatively minor sins of omission, where the analysis is almost certainly valid but where important details which would allow the reader to check the validity are ignored or else stated ambiguously; for example, the '±' symbol often appears in manuscripts with no indication of whether a standard deviation or a standard error is being reported. However, a proportion of the problems are more serious sins of commission, where inappropriate study design, analysis or interpretation throws considerable doubt onto the authors' conclusions.

In this article I give a set of guidelines for the preparation of manuscripts which I hope will help to reduce the large number of sins of omission. It is debatable to what extent a set of guidelines can help authors to avoid the sins of commission. Medical statistics is a subtle blend of methodology, experience and common sense (not unlike medicine!), and it is not simple to capture these nuances in a succinct set of guidelines. It is possible, however, to warn against the more common bad practices that appear, and indicate the situations where even the most numerate of clinicians should consider seeking professional statistical advice. In the guidelines I have attempted to distinguish between the relatively simple points of presentation, which are set out in some detail, and the more fundamental issues which are explored in an accompanying paper. The latter issues are more related to good research methodology, and these frequently give rise to problems in manuscripts submitted to *The British Journal of Surgery*.

While I have set out these guidelines with my experience of reading manuscripts and papers from *The British Journal of Surgery* very much to the fore, I have to acknowledge a debt of gratitude to the authors of two excellent and more general sets of guidelines for medical authors which have been published recently Bailar and Mosteller[3] have published a paper amplifying and explaining the extremely terse section on statistics in the *Uniform requirements for manuscripts submitted to biomedical journals* prepared by the International Committee of Medical Journal Editors[4], and Altman *et al.* have recently published an updated set of guidelines[5] based on a set published earlier by the same authors in *The British Medical Journal*[6]. For readers looking for a more comprehensive discussion of many of these issues I would recommend the excellent and eminently readable textbook by Bland[7].

Guidelines

These are set out under the headings of my earlier review[1], namely design, presentation, analysis and interpretation. To a large extent these areas overlap; for example, the interpretation may depend crucially on study design. However, any repetition should only serve to amplify the important points.

Design

Set out clearly the purpose of the study, identifying the *a priori* primary and secondary hypotheses[8].

Set out the reason for the choice of study design in terms of the purpose of the study[8].

Set out the reason for the choice of sample size, which should wherever possible be based on a power calculation. Report in addition whether the sample size was determined in advance or was chosen on the basis of repeated analysis of accumulating data[8].

Explain what measures were taken to control bias, whether this involved randomization, matching or an 'adjusted' statistical analysis.

In a randomized study, set out the actual mechanism that was used, and describe any form of blinding that was employed. Many studies are described as being randomized when in fact allocation was based on unit number or date of entry to the study. Such techniques do not constitute randomization, and can introduce serious bias between study groups.

Presentation of data: graphical

Wherever space permits, use a graphical presentation to illustrate the main findings of a study.

When the sample sizes are not too large, base the graph on the individual data points.

When 'before' and 'after' data are available on the same individual, either plot out both sets of data with lines linking values for the same individual[9], or else plot the changes.

If the data being presented are highly skewed, then consider using a transformation, such as plotting the data on a logarithmic scale.

If an analysis of the association between two continuous variables is central to the paper, then always include a scatter plot of the two variables plotted against each other.

When plotting survival curves or life tables, always indicate the number of individuals at risk at the various times of follow-up.

Avoid the use of 'error bars' showing one standard deviation or standard error (see below).

Presentation of data numerical

The use of a mean and standard deviation to describe a distribution is only appropriate when the distribution is (roughly) symmetrical or 'normal'.

For a skewed distribution, the median is better than the mean as a measure of the centre of the distribution.

For a skewed distribution, the interquartile range is better than the standard deviation as a measure of spread. Another possibility is to use the range itself, but this suffers from the disadvantages that it depends on the sample size, and is based on the most extreme (and hence perhaps suspect) observations.

Do not confuse the standard deviation and the standard error. Standard deviation is a measure of spread. For a variable

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with a normal distribution, roughly 95 per cent of the values will lie within two standard deviations of the mean. This range of mean plus or minus two standard deviations is the 95 per cent normal range, and does not depend on the sample size. Standard error is a measure of the precision of an estimated parameter, frequently an estimated mean. The precision of an estimate depends on the size of the sample on which the estimate is based, so that a small sample leads to a large standard error and a large sample leads to a small standard error. Under many common circumstances, one can be 95 per cent confident that the true value of a population parameter lies within two standard errors of its estimated value. This range of estimate plus or minus two standard errors is the 95 per cent confidence interval for the parameter. For technical details of how to obtain a confidence interval in general, see Gardner and Altman[10].

Avoid the use of the '±' symbol. The symbol is both confusing because it is often unclear whether a standard deviation or a standard error is being given, and misleading because it implies that the range of a value plus or minus one standard deviation or error has some special significance. From the above it should be clear that in general plus or minus two standard deviations or errors should be used. The former for a 95 per cent normal range (for a normal population) and the latter, under many circumstances, for a 95 per cent confidence interval.

Avoid spurious precision. Derived quantities are frequently reported to many decimal places, e.g. '$t = 3{\cdot}5426$' or '$P = 0{\cdot}2564$' or '40·74 per cent' (derived from 11 of 27). Such spurious precision detracts from the clarity of an exposition, and at least to me always suggests an uncritical transcription of a result from a computer printout to a manuscript. It is a clue to a statistical referee to look more critically at other aspects of the manuscript.

Percentages based on sample sizes of below 100 should always be given as integers, and for larger samples it suffices to give percentages to one decimal place. A sample mean should normally be given to one more significant figure than was used for the original measurements, and a standard deviation or error would be given to at most two more significant figures than was used for the original measurements.

Analysis

Account for all subjects recruited into the study, and attempt to assess any bias which might have been introduced through poor response rates or drop-outs and losses to follow-up.

Explain clearly which methods were used for which analyses. Simple, standard methods do not need to be explained in detail, but it is important to know, for example, whether the 't test' mentioned in the methods section was paired or unpaired. Sometimes it is unclear which analyses were used for which comparisons, for example if both the t test and the Mann–Whitney test are mentioned in the methods section This must be made explicit. Indeed it is often difficult to know where to set out the statistical methods, as a complex analysis does not fit in well with the conventional 'materials and methods, results and discussion' structure of a medical paper. For example, in a randomized study, a chance imbalance might be discovered in the age distribution of the study groups which needed to be incorporated into the analysis by way of a comparison 'adjusted' for age. How does one justify the method, before mentioning the 'result' of the age imbalance which required the adjustment? My own preference in such circumstances is to give a broad overview in the methods section and then to set out the statistical methods in detail in the results section, as each is used for the first time

Be aware of the assumptions underlying different tests, and do not make any assumptions which cannot be supported by the data All statistical procedures are based on a number of underlying assumptions. Most procedures assume that the observations being analysed are independent, an assumption which would be violated for example in a study where three tissue samples were collected for each subject[8]. The two sample t test as well as an assumption of independence requires the distributions being compared to be (roughly) normal, and requires the spread (standard deviation) of the two groups to be similar.

Strive to limit the number of statistical tests which are performed, and if multiple comparisons are unavoidable, use an appropriate adjustment to control the 'type I' (false positive) error[8]. Every time that a hypothesis ('significance') test is performed, there is a risk of reaching a false positive conclusion With the conventional threshold of $P = 0{\cdot}05$, this risk is one of 5 per cent, i.e one in 20. If a large number of tests are performed, it therefore becomes very likely that some false positive results will be obtained, which makes it difficult to interpret the results of multiple tests. The best approach is to identify *a priori* a primary hypothesis, and to give little weight to any secondary comparisons that are made. Such secondary findings might well generate interesting hypotheses to be pursued in further studies, but they cannot be regarded as being conclusive If it is not possible to identify a primary hypothesis, an alternative is to apply a correction for the multiple comparisons, and to demand a far more extreme threshold for the P value before claiming that a difference has been established. For example, with the Bonferroni correction, the P value is multiplied by the number of comparisons being made, and a finding is only accepted as being 'significant' if this adjusted value lies below 0·05. However, this leads to tests which have very low sensitivity, and represents a suboptimal approach to research.

When reporting the results of a statistical test, quote the value of the test statistic as well as the P value. For example, '$t = 1{\cdot}34$, 16 d.f., $P = 0{\cdot}20$' might be reported. Wherever possible give the actual P value, to two decimal places, rather than quoting, say, $P < 0{\cdot}05$. In particular, if the result is non-significant, always quote the actual P value rather than stating 'n.s.'. If the result is highly significant, it is sufficient to state that $P < 0{\cdot}001$ rather than quoting, say, $P = 0{\cdot}00004$.

Wherever possible present the results of a statistical comparison by reporting a confidence interval as well as or in place of the P value[8].

Do not use statistical tests to compare the baseline characteristics of study groups, but rather use adjusted analyses to investigate the effects of such imbalances[11]. A minor imbalance in a key prognostic factor can have a profound effect on a treatment comparison, even when the imbalance falls well short of 'significance'. Also a vast imbalance in a factor which is not related to outcome is of no relevance, even if the imbalance is highly significant.

Do not investigate 'subgroup' effects by literally making comparisons within subgroups of subjects Test instead for an interaction, i.e. a treatment effect which varies systematically with the value of a characteristic such as age or stage of disease[8].

Interpretation

Do not confuse statistical significance with clinical relevance. Use confidence intervals to assess clinical relevance, especially when interpreting a 'negative' finding[8].

Do not place undue emphasis on a secondary analysis, especially if the analysis was suggested by an inspection of the data[8].

Be very wary of implying causality in anything other than a controlled randomized trial. Association does not imply causation.

Avoid any imprecise use of technical terms For example, do not discuss the 'correlation' between two variables when what is meant is 'association'.

Point out and discuss any weaknesses in study design or execution. An honest evaluation of a study carries more weight than an attempt at concealment!

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Accuracy of endosonography in the staging of rectal cancer treated by radiotherapy

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Endosonography is the best available method for the pretherapeutic staging of rectal cancer. The present prospective study was to determine the influence of previous radiotherapy, widely used in the management of this tumour, on the accuracy of endosonography. A complete endosonographic examination was performed just before surgery in 40 patients with rectal cancer. Endosonographic and pathological staging were compared in group A, 21 patients without previous radiotherapy, and group B, 19 patients with preoperative radiotherapy. While the endosonographic accuracy for lymph node involvement was similar in the two groups (85 per cent compared with 84 per cent), wall invasion was correctly ascertained in 86 per cent in group A but in only 47 per cent in group B ($P<0\cdot05$)*. After irradiation, the thickening of the rectal wall and the poor visualization of the hyperechoic layers hampered interpretation. Post-radiotherapy inflammation and/or fibrosis probably explained the echographic changes. Radiotherapy therefore altered endosonographic staging of rectal cancer. New interpretation criteria are needed for evaluation and follow-up of rectal cancer treated by radiotherapy.*

Endosonography has been used for several years in the pretherapeutic staging of rectal cancer[1]. Assessment of wall invasion and metastatic lymph nodes is better than with other imaging techniques[2–4] and is so efficacious that treatment might now be altered according to endosonographic staging. Endosonography could also be of importance for the follow-up of anastomoses after surgery to detect submucosal recurrences[5].

Radiotherapy is currently used in rectal cancer either with curative intent in small tumours[6] or in association with surgery in larger tumours[7–9]. In this setting, endosonography could be of interest in ascertaining the efficacy of radiotherapy, to detect and stage recurrences after radiotherapy alone, or to detect anastomotic recurrences after anterior resection associated with radiotherapy, even if recurrence frequency is decreased by radiotherapy. However, it has not yet been proven that endosonographic staging is accurate when patients have been previously treated by radiotherapy. In this study, endosonographic accuracy was ascertained in patients with rectal cancer managed with preoperative radiotherapy. Comparison with a group of patients treated during the same period by surgery alone showed that radiotherapy significantly hampered the assessment of wall invasion by endosonography.

Patients and methods

From November 1987 to June 1989, 51 patients with rectal cancer diagnosed by colonoscopy with biopsies were examined by intrarectal endosonography just before surgery. Forty were left in the study, as endosonographic examination was incomplete in 11 patients with tight stenosis caused by the tumour. Surgery in the 40 patients with complete examination consisted of: anterior resection in 16, abdominoperineal excision in 23 and peranal local excision in one. The patients were divided into two groups: in group A (21 patients) no preoperative treatment was given; in group B (19 patients) radiotherapy was performed before endosonographic examination. Indications for radiotherapy were twofold: (1) preoperative external irradiation in 16 patients with a large tumour at pretherapeutic evaluation; radiotherapy (30–46 Gy) was then given within 2 months of surgery; (2) curative external and intracavitary irradiation in three patients with a small tumour at pretherapeutic evaluation. Surgery was considered 1 year later when local recurrence occurred. Thus in the first group endosonography closely followed radiotherapy, while in the second group it was separated by several months.

The characteristics of the patients in the two groups are summarized in *Table 1*. While the groups were not randomized, they were roughly similar as indications for radiotherapy were chosen by the referring physicians according to their pretherapeutic evaluation and their usual practice of radiotherapy. It should be noted that only seven of the 16 patients treated by preoperative irradiation had initial endosonography before radiotherapy.

All the ultrasound examinations were performed using an ultrasound scanner type 1846 (Bruel and Kjaer, Denmark) with a rotating hand-held endoprobe and two transducers of 4 and 7 MHz (focal lengths 1–4 and 2–5 cm respectively). Digital examination and rigid rectoscopy preceded the blind introduction of the endoprobe. After placement in the lumen, the latex balloon, which surrounds the transducer, was filled with deaerated water. The five layers of the rectal wall were interpreted according to Hildebrandt *et al.*[5]: first layer (hyperechoic) = interface between the balloon and the mucosa; second layer (hypoechoic) = mucosa and submucosa; third layer (hyperechoic) = interface between submucosa and muscularis propria; fourth layer (hypoechoic) = muscularis propria; and fifth layer (hyperechoic) = interface between muscularis propria and perirectal fat. Ultrasonic prediction of wall involvement was based on the ultrasonic tumour node metastasis classification (uTNM): uT_1 tumour confined to the mucosa and submucosa, uT_2 tumour invading the muscularis propria but confined to the rectal wall, uT_3 tumour penetrating into the

Table 1 *Characteristics of patients in group A (no previous radiotherapy) and group B (previous radiotherapy)*

	Group A ($n=21$)	Group B ($n=19$)
Female:male	9:12	6:13
Age range (median) in years	38–78 (66)	44–80 (67)
Range of lower limit of rectal cancer from anal margin (range) in cm	2–11 (5)	3–8 (6)
pTNM classification		
$T_0/T_1/T_2/T_3/T_4$	0/3/6/10/2	1/1/8/8/1
N_0/N_+	12/8	14/5

pTNM, pathological tumour node metastasis staging

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perirectal tissues without involvement of the surrounding organs, uT_4 tumour penetrating into surrounding organs. Hypoechoic circumscribed structures in the mesorectum were considered as metastatic lymph nodes (uN_+).

Operative specimens were staged according to the new pathological TNM classification (pTNM)[10]. A tumour was staged pT_0 when no residual tumoral cells were found after radiotherapy. The uTNM and pTNM stagings were compared in the two groups. Statistical evaluation was performed using the χ^2 test.

Results

Assessment of wall invasion (Table 2)

The accuracy of endosonography was 86 per cent in group A (18 of 21) but only 47 per cent in group B (9 of 19) ($P<0{\cdot}05$). In group A, two tumours were overstaged and one understaged, while in group B, six were overstaged and four understaged. It is worthy of note that one tumour, eradicated by preoperative radiotherapy (pT_0), was staged uT_3 by endosonography (*Figure 1*).

Pathological examination of the operative specimen showed that, in understaged tumours of both groups, invasion of the perirectal fat by neoplastic cells was limited. In the two overstaged cases in group A, the tumour was limited to the muscularis propria but invaded the whole muscular layer. While moderate inflammation was noted in tumours of patients of group A, inflammation and fibrosis were found to a greater extent in all patients of group B, and were especially marked in the six patients overstaged by endosonography. On the other hand, pathological examination of tumour after radiotherapy was sometimes difficult; in one patient staged uT_4 initial pathological examination suggested a pT_1 tumour with very marked fibrosis in the muscularis propria and the perirectal fat (*Figure 2*), but careful examination of new serially cut sections showed limited islands of neoplastic cells in the prostatic wall which led to a pT_4 stage.

Table 2 *Determination of wall invasion by endosonography (uT) in the two groups of patients compared with the pathology of the operative specimen (pT)*

	Group								
	A ($n=21$)				B ($n=19$)				
	pT_1	pT_2	pT_3	pT_4	pT_0	pT_1	pT_2	pT_3	pT_4
uT_1	3					1			
uT_2		4	1				3	4	
uT_3		2	9		1		5	4	
uT_4				2					1

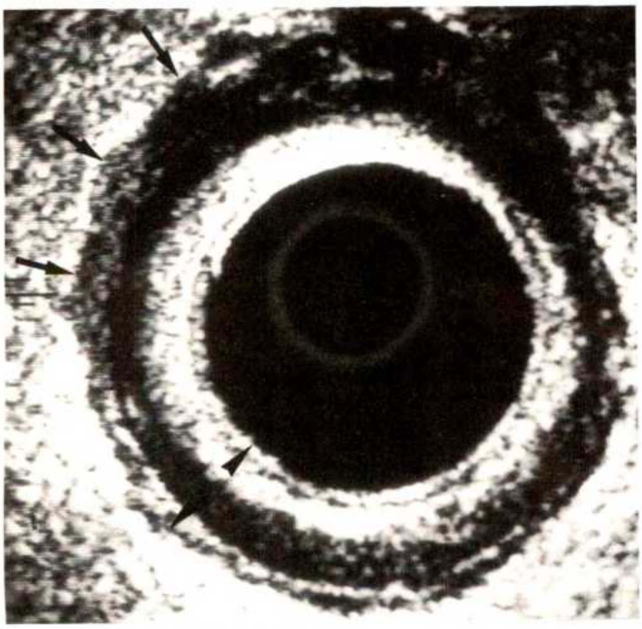

Figure 1 *Rectal cancer after radiotherapy: endosonographic staging was uT_3 but on pathological examination the tumour had been eradicated. Arrows, irregular outer margins; arrowheads, thickened wall*

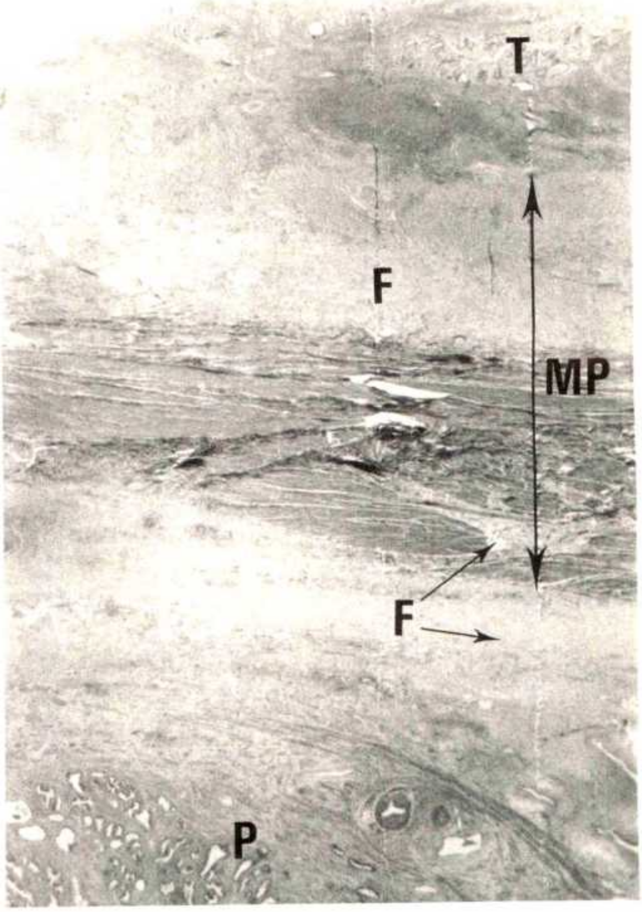

Figure 2 (*haematoxylin, phloxine, safran; original magnification* × 6). *Rectal cancer after radiotherapy: pathology of rectal wall and perirectal tissue. T, residual tumour; F, fibrosis; MP, muscularis propria; P, prostate*

Table 3 *Determination of metastatic lymph nodes by endosonography (uN) in the two groups of patients compared with pathology of the operative specimen (pN)*

	Group			
	A ($n=20$)		B ($n=19$)	
	pN_0	pN_+	pN_0	pN_+
uN_0	11	2	13	2
uN_+	1	6	1	3

N_0, no metastatic lymph nodes; N_+, at least one metastatic lymph node

Assessment of lymph node involvement (Table 3)

One patient of group A was not staged (local tumour excision only). Thus 20 patients were evaluable in this group. The accuracy for predicting metastatic lymph nodes was 85 per cent, the sensitivity 75 per cent, the specificity 92 per cent, the positive predictive value 86 per cent, and the negative predictive value 85 per cent. In group B the accuracy was 84 per cent, the sensitivity 60 per cent, the specificity 93 per cent, the positive predictive value 75 per cent, and the negative predictive value

87 per cent. Therefore the overall results were similar in both groups. In the group with preoperative radiotherapy, pathological examination of metastatic lymph nodes showed that some of them were partly fibrosed; sometimes only little neoplastic islands persisted in the fibrosis. This was not observed for lymph nodes in patients of group A.

Discussion

Different authors have shown that endosonography is very accurate in the assessment of the depth of wall invasion in patients with rectal cancer operated on without previous treatment[3,11–19]. The present results (accuracy 85 per cent) in group A are similar to those found in the literature.

Only one series of endosonography in rectal cancer has included patients with previous radiotherapy[20]. However, the number of such patients was too limited to allow definite conclusions concerning the effect of irradiation on endosonographic results. Of note, in the present study, when endosonography was performed after radiotherapy its accuracy was much lower at 47 per cent ($P < 0{\cdot}05$). While the two groups were not randomized, their main characteristics were similar and could not obviously explain this discrepancy. One of the most important drawbacks in endosonographic staging[16] is the distinction between T_2 tumour invading most of the muscularis propria and T_3 tumour which slightly invades the perirectal fat. Indeed all the errors but one in this study were understaging of small pT_3 tumours (five cases) or overstaging of pT_2 tumours (seven cases).

The proportion of such mistakes was much higher in group B than in group A (56 per cent compared with 19 per cent). This high rate could be explained by the modifications of the echopattern of the rectal wall after radiotherapy, an observation already made in oesophageal squamous cell carcinomas treated by radiotherapy[21]. After irradiation, the rectal wall was thickened, more hypoechoic, and the different layers less clearly visualized. The outer limit of the rectal wall was especially hard to delineate. The best illustration of the difficulties in endosonographic interpretation was shown by the tumour staged uT_3 which was in fact eradicated on pathological examination. Inflammation and fibrosis induced by preoperative radiotherapy and clearly evidenced by pathological examination were probably responsible for these changes of echopatterns. It must be emphasized that in the uT_4 staged tumour, fibrosis (*Figure 2*) was again more probably responsible for the endosonographic picture than the limited islands of tumour cells found only on the second careful pathological examination. This case also underlines the need for careful pathological studies before concluding total tumour destruction by preoperative radiotherapy.

There was no clear effect of the time interval between the end of radiotherapy and the endosonographic examination. When the irradiation was performed as early as 1 year before echography, there was again fibrosis that could have explained the two overstagings in the three affected patients. No conclusions could be drawn about longer intervals from this study.

For the diagnosis of metastatic lymph nodes, the present results are comparable in the two groups and with those reported by others[3,5,12,14,17,19,22]. Thus there was a striking difference between the deleterious effect of radiotherapy on endosonographic interpretation of wall invasion and of lymph nodes. Several points related to this discrepancy should be considered.

First there is the fibrotic involution of metastatic lymph nodes after radiotherapy. Pathological examination showed that metastatic lymph nodes in patients treated by radiotherapy were progressively replaced by fibrosing tissue, perhaps after a volume reduction (*Figure 3*). Thus the nodes, more hypoechoic, could be more easily visualized at endosonography. Second, the limited number of patients with metastatic lymph nodes (respectively eight and five in groups A and B) may not have allowed a significant difference to be shown. Third, one should consider the possible disappearance of inflammatory lymph nodes which could induce a false positive result.

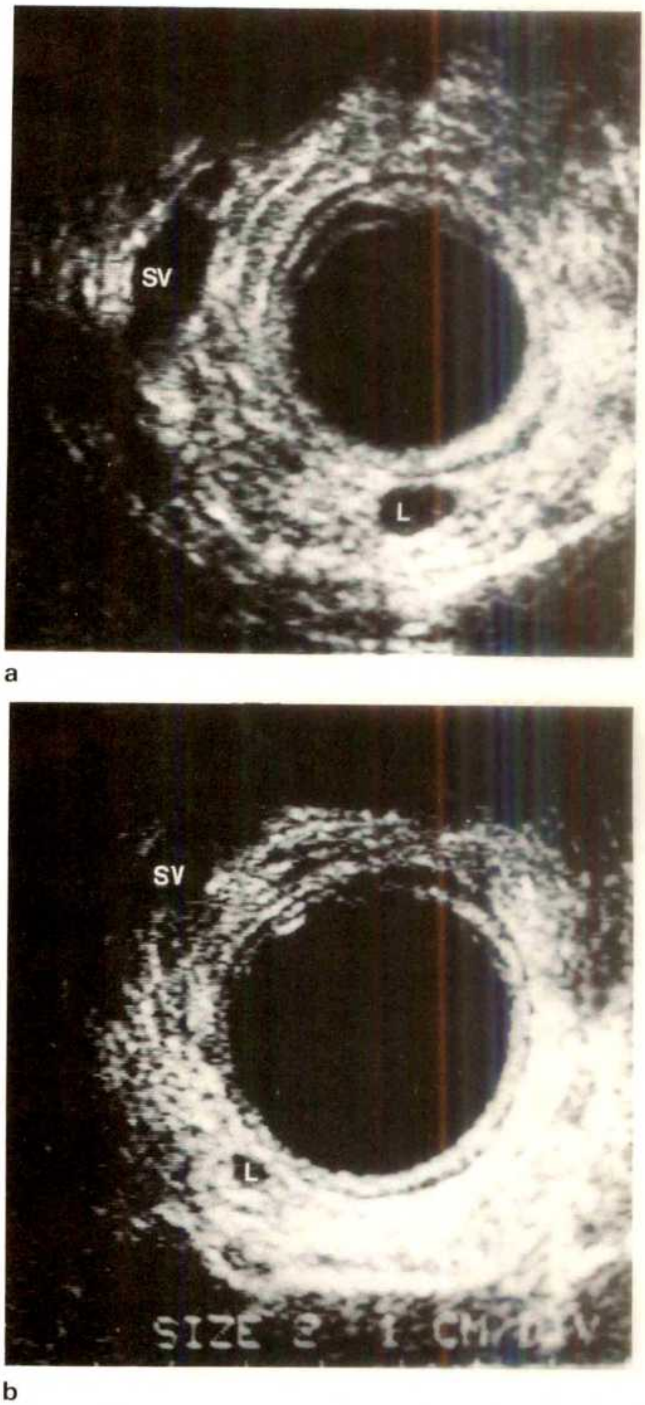

Figure 3 *Size reduction of a lymph node after radiotherapy as shown by endosonography.* **a** *Endosonographic appearance before irradiation.* **b** *Endosonographic appearance after irradiation. SV, seminal vesicle; L, lymph node*

There is no clear evidence from published studies on the evolution of lymph nodes after radiotherapy in rectal cancer that their number is reduced. Some studies have shown that both normal and pathological lymph tissue have been reduced by irradiation[23,24] but the lymph node harvest in resected specimens was not optimal, limiting the value of the conclusions.

Thus new techniques (high frequencies, ultrasound guided aspiration cytology) or new interpretation criteria are necessary for endosonographic evaluation of rectal cancer treated by radiotherapy. After surgery, it is known that interpretation of the anastomotic wall (thickened, hypoechoic) is difficult. It has been suggested that endosonographic examination be performed shortly after surgery and thereafter, with consideration being given only to modifications in the echopatterns at follow-up examinations. Similarly, it would perhaps be useful for proper interpretation to compare endosonographic findings before and after radiotherapy.

In conclusion, the assessment of rectal cancer staging by endosonography was hampered by previous radiotherapy, even when this was performed as long as 1 year before sonographic examination. Distinction between T_2 and T_3 tumours became more difficult and tumour extension can be much overestimated because of inflammation and fibrosis secondary to radiotherapy. On the other hand, the interpretation of lymph node involvement seems to be unaffected. Similar studies are now necessary to ascertain the accuracy of endonosography in the detection of anastomotic recurrence in patients treated by surgery and pre-, per- or postoperative radiotherapy.

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Comparison of morbidity and function after colectomy with ileorectal anastomosis or restorative proctocolectomy for familial adenomatous polyposis

Restorative proctocolectomy with an ileal reservoir (RPC) should prevent colorectal cancer in patients with familial adenomatous polyposis. Until this is confirmed its role compared with total colectomy and ileorectal anastomosis (IRA) will depend on the relative morbidity and postoperative bowel function after the two procedures. This was analysed in 99 patients (37 RPC, 62 IRA) operated on between 1977 and 1989. Morbidity was greater after RPC with subsequent ileostomy closure (median hospital stay, 24 versus *11 days; complications, 60* versus *21 per cent; reoperation, 29* versus *3 per cent; return to normal activity, 31* versus *14 weeks). There was little difference in bowel function; after IRA median frequency was 3/24 h and urgency (unable to wait 15 min) occurred in 50 per cent, compared with 4·5/24 h and 17 per cent after RPC. Night evacuation occurred in 10 and 43 per cent respectively. IRA was performed in younger patients (median 19* versus *31 years) who had fewer bowel motions before operation (2* versus *5/24 h). The greater morbidity of RPC suggests that it should be restricted to patients at higher risk of developing later rectal cancer, including those unavailable for follow-up and those with large or confluent rectal polyps or with curable colon cancer at the initial colectomy.*

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The conventional operation to prevent large bowel cancer in patients with familial adenomatous polyposis is colectomy with ileorectal anastomosis (IRA) followed by endoscopic destruction of rectal adenomas. Because cancer still occurs in the rectum even if it is closely monitored[1–3], restorative proctocolectomy with ileal reservoir (RPC) has been advocated[4,5] because it should prevent colorectal cancer by removing all the large bowel mucosa. Disadvantages include greater technical complexity and the need for a temporary ileostomy. The prevention of large bowel cancer has yet to be confirmed.

The outcome of these two operations has therefore been studied with reference to morbidity, bowel function and social activity in patients treated by surgeons from one institution.

Patients and methods

The first RPC for familial adenomatous polyposis at the hospital was performed in July 1977. All patients having RPC or IRA from that time until December 1989 were considered for the study (*Table 1*).

Colectomy with IRA was the usual procedure adopted by most surgeons and 62 such patients were studied (*Table 1*). Thirty-seven patients underwent RPC. Thirteen (35 per cent) had previously undergone colectomy, with an IRA in 11 and a colorectal anastomosis and a coloanal anastomosis in the remaining two patients. RPC was performed because of uncontrollable rectal adenomas in seven, rectal cancer in three, the surgeon's policy in two, and referral specifically for RPC in one. The indications for the remaining 24 RPCs were uncontrollable rectal polyps in three, rectal cancer in four (of whom two had uncontrollable rectal polyps), colonic cancer in five (one with uncontrollable rectal polyps), the surgeon's policy in 11, and referral specifically for RPC in one. The median age of the patients undergoing RPC was 12 years greater (31 *versus* 19, $P<0{\cdot}001$). The mean duration of follow-up after RPC was not significantly different from that after IRA (5·2 *versus* 6·5 years).

Hospital records were used to assess morbidity in the perioperative period and subsequent treatment related to the operation or the large bowel component of the disease. Patients were recalled for interview if ileostomy closure after RPC or the IRA had been performed more than 3 months previously. Patients were questioned by one of three staff members of the Polyposis Registry using a standard proforma and not by any surgeon involved in their treatment. Those unable to attend were interviewed by telephone or asked to return a questionnaire.

Surgical morbidity was assessed by the number of days spent in hospital after operation and by complications identified in the case

Table 1 *Patients undergoing restorative proctocolectomy or ileorectal anastomosis from 1977 to 1989*

	No. of patients		
	Restorative proctocolectomy		
	First operation	Second operation	Ileorectal anastomosis
Treated	38		82
Not studied			
Emigrated	1		3
Died			6
Other reasons			11
Patients studied	24	13	62
Men/women	10/14	8/5	33/29
Age (years)			
Median	31*		19*
Range	14–52		12–53
Follow-up (years)			
Mean	5·2		6·5
Range	0·7–12·2		0·7–12·8
Reviewed for			
Treatment morbidity	23	11	62
Bowel function	18	12	61

* $P<0{\cdot}001$, Wilcoxon signed rank test

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Table 2 *Postoperative stay (days)*

	Restorative proctocolectomy					
	As first operation		As second operation		All cases (both operations)	Ileorectal anastomosis
	RPC	Stoma closure	RPC	Stoma closure		
Median	17	10	12	14	24*	11*
Range	10–43	6–33	9–20	8–53	17–63	8–44

* $P<0.001$, Wilcoxon signed rank test

Table 3 *Complications*

	Restorative proctocolectomy						
	As first operation		As second operation		All cases		
	RPC	Stoma closure	RPC	Stoma closure	RPC	Stoma closure	Ileorectal anastomosis
Cases reviewed	23	21	13	12	36	33	62
Bowel obstruction		2	1 (1)	4 (2)	1 (1)	6 (2)	7
Anastomotic defect	3				3		1 (1)
Pelvic abscess	1		2		3		1
Anastomotic stricture	1 (1)				1 (1)		1 (1)
Stomal retraction	1 (1)				1 (1)		
Intra-abdominal bleed	2 (2)				2 (2)		
Gastrointestinal bleed	1				1		
Pus in pouch	1				1		
Wound infection							2
Repeat mucosectomy		1 (1)				1 (1)	
Deep venous thrombosis			1		1		1

Values in parentheses show patients who required operation

notes. The morbidity of subsequent treatment was measured by the number of outpatient visits and by days spent in hospital for treatment of large bowel disease.

The χ^2 test with Yates' correction was used to compare proportions for large samples and Fisher's exact test for small samples. Normally distributed data were compared by Student's *t* test. Variables not normally distributed were compared using Wilcoxon's signed rank test. A distribution with less than a 5 per cent likelihood of being due to chance was accepted as significant. Data in the tables show the mean value if the variable is normally distributed and the median if not. Denominators vary because not all data were obtained for every patient.

Results

Morbidity

Details of the length of hospital stay after operation and of complications are given in *Tables 2* and *3*.

There were no deaths in hospital or within 30 days of surgery. RPC was followed by a longer postoperative stay and by closure of the temporary ileostomy after an average of 70 days. The combined postoperative stay after RPC and ileostomy closure was more than twice as long as that after IRA (24 *versus* 11 days). This was associated with a higher complication rate (60 per cent RPC *versus* 21 per cent IRA). The likelihood of reoperation was higher after RPC (29 *versus* 3 per cent). These risks differed significantly (complications, $P<0.0002$; reoperation, $P<0.01$). In patients undergoing RPC, closure of the ileostomy accounted for seven of the 21 complications (33 per cent) and three of the eight operations performed for complications (38 per cent).

A comparison of the first cohort of 12 patients who had RPC as their first operation with the second 11 cases showed that the median postoperative stay including ileostomy closure fell significantly, from 35 to 23 days ($P<0.02$).

There was no significant difference in the rate of attendance as outpatients between the two groups (median 2·8 visits/year for RPC *versus* 2·1 visits for IRA). Of the patients with an IRA, 27 (44 per cent) needed treatment for rectal polyps (removing only adenomas over 5 mm in size or areas of confluent adenomatous change) over a mean follow-up period of 6·5 years. Patients were admitted on a mean of 2·5 occasions, usually for 3 days.

Bowel function

Details of bowel function are given in *Table 4*. For all patients having a restorative proctocolectomy (those having it as first and second operation combined), return to normal activity occurred at a median of 31 weeks. Median frequency of defaecation in the combined group was 4·5 and 17 per cent were unable to delay defaecation for more than 15 min.

The frequency of defaecation before surgery in patients having RPC was greater than in those having IRA. However, IRA increased bowel frequency and was more often associated with urgency, although patients who had RPC more often had to get up at night to defaecate. After RPC, patients took twice as long to resume all their normal activities. There was no difference between the two operations in the proportion of cases using constipating drugs, experiencing anal leakage or irritation, wearing a pad, or noting an adverse effect on diet, work or social activities.

Three men and three women noted diminished libido after RPC, which continued until after ileostomy closure. None

Table 4 *Effect of operation on bowel function and other activities*

	Restorative proctocolectomy			
	As first operation	As second operation	Ileorectal anastomosis	*P*
Patients studied	20	13	62	
Stools/24 h (median (range))				
Preoperative	5·0 (1–20)	5·4 (2–10)	2 (0·5–20)	0·03†
Postoperative	5·1 (2–15)	3·9 (1·5–8)	3* (1–11)	0·001†
Night evacuation	9/20 (45%)	4/10 (40%)	6/61 (10%)	0·001†
Can delay defaecation > 15 min	17/20 (85%)	7/9 (78%)	31/62 (50%)	0·008†
Antidiarrhoeal medication	7/20 (35%)	2/9 (22%)	10/60 (17%)	0·2
Continence				
Normal	12/20 (60%)	6/10 (60%)	43/60 (72%)	0·3
Wear pad	1/20 (5%)	2/10 (20%)	0/24	0·1
Anal irritation	17/20 (85%)	6/10 (60%)	37/60 (62%)	0·2
Avoid some foods	11/20 (55%)	4/10 (40%)	29/60 (48%)	0·9
Factors compromised by operation				
Work	5/20 (25%)	0/8	3/60 (5%)	0·1
Social life	5/20 (25%)	0/8	9/60 (15%)	0·9
Sexual activity	5/15 (33%)	1/9 (11%)	0/50	0·001†
Weeks until normal activity resumed (median (range))	33 (6–98)	26 (4–52)	14 (2–52)	0·002†

* Significant postoperative increase

† Significant difference between result after ileorectal anastomosis and result after all restorative proctocolectomies combined

reported failure of erection, ejaculation or orgasm. At the time of interview problems in all but one case had completely resolved. One man continued to complain of partial loss of erection, but had a history of pancreatitis and required high-dose analgesia.

Four patients who had a triplicated ileal reservoir constructed before 1982 regularly emptied the pouch by intubation and one further patient catheterized intermittently. The remainder defaecated spontaneously.

Discussion

The two groups of patients differed in three important respects. Those who underwent RPC were more than ten years older. Before surgery, those who had not already had a colectomy and then proceeded to RPC had a frequency of defaecation more than twice that of patients having IRA. IRA was a widely practised and standard operation, but RPC was not.

During the 12 years of patient accrual the complication rate of RPC fell and changes in reservoir design improved the functional results. The interpretation of this analysis should take these factors into account.

Although most surgeons construct a temporary ileostomy during RPC[6] it may cause morbidity[7] and it has been suggested that a stoma can safely be omitted in a fit patient if the procedure is technically easy[8]. Most patients with polyposis satisfy these criteria. The presence of an ileostomy caused two of the 14 complications in the present series, and a further seven complications occurred after ileostomy closure. Nine of 21 postoperative problems were therefore ascribed to the ileostomy. These did not impair the long-term results of the operation but must be balanced against the value of a stoma in reducing pelvic sepsis should the anastomosis leak. A leak occurred in only three of the 37 patients, and currently occurs in less than 10 per cent of patients undergoing RPC[9].

IRA increased stool frequency; RPC did not. Patients having RPC as their first operation had more frequent stools before surgery, perhaps owing to severe rectal disease, and the operation did not alter this. Urgency was, however, less common, suggesting good reservoir function.

The diminished libido reported by five patients after RPC until ileostomy closure may reflect the longer convalescence required with RPC compared with IRA.

There was no difference in the frequency of outpatient visits after the two operations. After IRA a digital examination and sigmoidoscopy at least every 6 months are recommended[10] and treatment for rectal polyps was performed in 44 per cent of patients with IRA. Outpatient or day-case endoscopic polypectomy would have obviated the need for the 3 days in hospital required for each treatment.

Polyps are found in anorectal mucosa 'strippings' in almost all cases[11]. RPC should prevent rectal cancer by removing the affected mucosa completely. Adenomas have formed in two patients in the series but they have also been reported in Kock reservoirs[12] and in the terminal ileum above a straight ileoanal reconstruction[13] and an ileorectal anastomosis[14,15] as well as in a conventional ileostomy[14]. Ileal cancer in these circumstances is very rare and it should not be more common in the ileoanal reservoir. Dysplastic changes do not occur in Kock pouches after 16–20 years[16].

In view of the additional morbidity of RPC and the usual need for a temporary ileostomy, RPC should be restricted to patients at increased risk of rectal cancer. Rectal cancer is more likely if large rectal polyps are not removed[17]. Of patients followed at St. Mark's Hospital after IRA, 9 per cent developed rectal cancer during a similar period[1]. At the Mayo Clinic, cancer resected at or before colectomy for polyposis has also correlated significantly with subsequent rectal cancer[3]. A correlation exists between the subsequent development of rectal carcinoma and the number of rectal polyps[3], and confluent adenomatous change in the rectum may be a relative indication for RPC. After colectomy and ileorectal anastomosis, however, rectal polyps regress in some patients[18].

In conclusion, a patient without large bowel cancer who is available for follow-up and who does not have large or confluent rectal adenomas should have a colectomy and IRA. A patient unavailable for follow-up or with a rectum severely affected by adenomatosis or with curable cancer in the colon or upper rectum should have RPC. If rectal excision becomes necessary after IRA, a salvage RPC is feasible unless there is cancer in the lower rectum. Colectomy with IRA is the procedure of choice in adolescent patients identified by screening. Recovery is rapid, morbidity is low and function is good, and the cancer risk is very low.

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Use of the ultrathin choledochoscope in cholecystectomy

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Use of the ultrathin choledochoscope (2 mm) was evaluated in 80 patients undergoing routine cholecystectomy. It was used successfully in 67 (84 per cent) patients. There were eight (12 per cent) explorations of the common bile duct and no negative explorations. The instrument was helpful in determining the nature of an equivocal on-table cholangiogram. The ultrathin choledochoscope may be useful in reducing the rate of negative common bile duct exploration.

Despite the use of routine operative cholangiography, the rate of negative common bile duct exploration remains at a level of 22–33 per cent[1,2]. Common bile duct exploration has an associated morbidity rate of the order of 45 per cent and a mortality rate of 7·4 per cent in older patients[1,3]. The mortality rate is especially high when patients present with jaundice, pancreatitis and cholangitis[1,3,4], but even after negative common bile duct exploration the mortality rate is at least double that of cholecystectomy alone[4]. In this latter group Sheridan *et al.* found a mortality rate of 3·6 per cent directly attributable to complications arising from opening the bile duct. They also found that the morbidity rate from negative duct exploration was 39·3 per cent[1].

It follows therefore that any method that could safely reduce the rate of common bile duct exploration would be important. We evaluated the ultrathin choledochoscope to provide choledochoscopy via the cystic duct.

Patients and methods

Eighty patients were studied, 58 women and 22 men (age range 24–81 years, median 57 years). All patients underwent routine elective cholecystectomy. During the procedure all 80 patients had an on-table cholangiogram, performed by cannulating the cystic duct and injecting first 3 ml then 5 ml of contrast (Conray 280, May and Baker, Dagenham, UK). More contrast was used if the common bile duct appeared dilated. The cystic duct was then cannulated with the ultrathin choledochoscope. The endoscopic findings and the time taken to perform the procedure were recorded.

The instrument used was the 2 mm semiflexible fibreoptic choledochoscope (Microvasive Inc., Milford, Massachusetts, USA) (*Figure 1*). The method has been previously described[5]. Although the instrument is intended to be disposable, we have resterilized it with its non-disposable eyepiece. The endoscope is soaked in glutaraldehyde 5 per cent (ASEP; Galen, Portadown, UK) for 30 min then washed in saline before use. The cost of ASEP is £1.75 for 5 l and this can be reused, reducing the cost of the technique. This method meets the requirements for safety standards in sterilizing endoscopes[6]. The instrument is semiflexible but has no internal controls. Control of the instrument is achieved by grasping the instrument between thumb and forefinger outside the bile duct. It can be further angulated by the insertion of a stiffening wire, which can also be used as a guide wire to aid insertion into the cystic duct. Saline is then infused down a channel in the endoscope into the common bile duct. This prevents the duct from collapsing and ensures a good view. The end-point of endoscopy was the visualization of the duodenum. The endoscope was designed to be diagnostic, not therapeutic.

Results

The cystic duct was successfully cannulated in 69 (86 per cent) cases. However, due to the spiral valve of Heister, the instrument could be advanced into the common bile duct in only 67 (84 per cent) cases. In these 67 patients excellent views of the distal part of the biliary tree were obtained. On only 38 occasions (48 per cent) was it possible to negotiate the instrument proximally to inspect the common hepatic duct. Failure to visualize the hepatic duct was related to the site and angle of insertion of the cystic duct. The fibres of the endoscope were broken on 13 occasions; thus, 14 endoscopes were used in all, a mean of only six uses per endoscope. The time taken to perform choledochoscopy ranged from 3 to 15 min (median time 6 min). Of the 80 patients studied, 67 had both successful endoscopy and cholangiography; 53 were normal by both methods, and in five patients stones were detected by both methods. These five patients had the common bile duct explored and stones removed.

There were nine equivocal cholangiograms. In these patients the endoscope was helpful in confirming the presence or absence of common duct stones (*Table 1*). In six of these nine patients

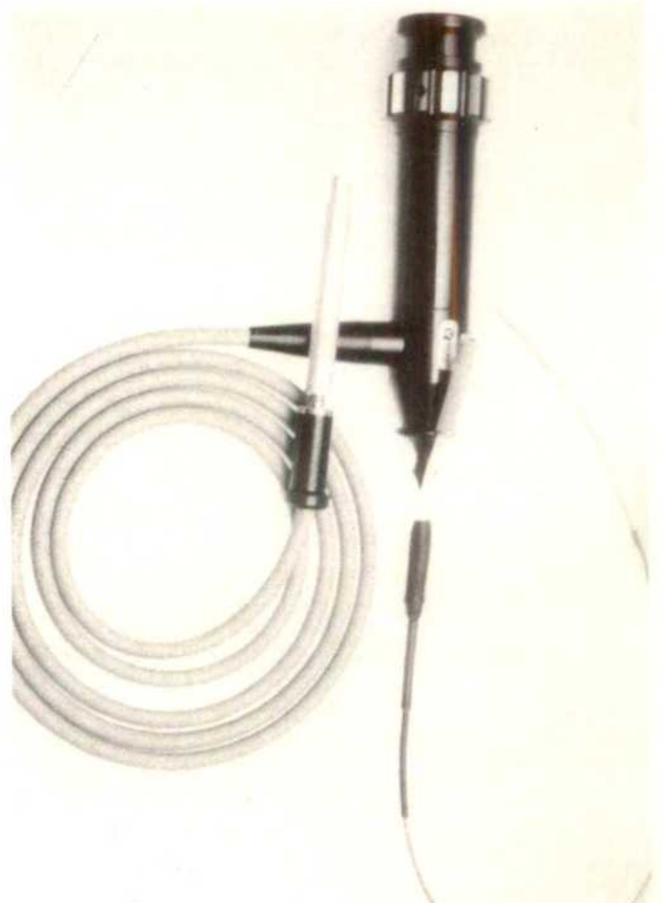

Figure 1 *The ultrathin choledochoscope 2 mm*

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Table 1 *Endoscopic findings in nine patients with operative cholangiograms that were difficult to interpret*

Cholangiography		Endoscopy	
n	Findings	*n*	Findings
4	No flow into the duodenum	3 1	Normal endoscopy Stone seen
4	Equivocal filling defects	2 2	Normal endoscopy Stones seen
1	Duodenal diverticulum	1	Normal endoscopy

the endoscopy was normal and these patients were spared a probable common bile duct exploration. In all, eight patients (12 per cent) had common bile duct exploration for stones; there were no negative explorations. There were no complications attributable to the use of the instrument, and mean follow-up is now 23 months. All patients remain well.

Discussion

The decision to explore the common bile duct is of major importance to the patient, as duct exploration is usually associated with a significant increase in morbidity and mortality rates compared with cholecystectomy alone[1,3,4]. Many of the complications reported after duct exploration are related to septic complications occurring in patients with stones in the duct[1], and it might be argued that a negative duct exploration is not paticularly dangerous. However, pancreatitis, bile leakage, biliary fistula and T tube complications are just as likely to follow a negative exploration as a positive one. Doyle *et al.*[4] showed that a major reason for the fall in mortality rate from cholecystectomy over a 25-year period was the reduction in unnecessary common bile duct explorations. The mortality rate from negative duct exploration in their study was twice that from cholecystectomy alone. Vellacott and Powell[3] found a mortality rate of 7·6 per cent for exploration when stones were found and 6·8 per cent for negative exploration, although all their patients were over 70 years old and a significant number had exploration via a transduodenal approach. Sheridan *et al.*[1] reported an overall mortality rate for duct exploration of 4·1 per cent in the over-65 age group, the mortality rate below this age being similar to that for cholecystectomy alone at 0·6 per cent. In this series the mortality and morbidity rates from negative exploration were 3·6 and 39·3 per cent respectively. It would therefore appear to be important to avoid a negative duct exploration if possible, particularly in the older patient.

The reasons for the high negative exploration rates are the unreliability of classical clinical criteria and poor cholangiography resulting in a large number of false positive or equivocal cholangiograms. Stubbs and Blumgart[7] found that, in 14 patients who had negative explorations, seven were the result of failed or inadequate cholangiography. They also showed, in a departmental study, that 33 per cent of cholangiograms were not of diagnostic quality.

It seems, therefore, that as standard cholangiography is unreliable a further adjunct to the diagnosis and determination of an equivocal cholangiogram is needed.

Fluoroscopy has been the most commonly used refinement, but Stubbs and Blumgart still had a negative exploration rate of 28 per cent when this technique was used[7]. Others have found the technique to be of greater value, and in one series the rate of negative exploration was only 6 per cent[8]. In a small pilot study[9] digital subtraction cholangiography was extremely accurate at predicting the presence or absence of stones in the duct, but this equipment is not available in the majority of theatres. The use of antispasmodic drugs may clarify the cholangiogram that shows no flow of contrast into the duodenum and might have been of value in some of our patients, but it is not always successful[10].

Choledochoscopy via the cystic duct was first described by Nghiem[11] using an instrument of 6·5 mm diameter which was inserted after dilatation of the cystic duct. We have previously reported on the feasibility of using ultrathin endoscopes of 2 and 2·5 mm diameter respectively[5,12], which can be passed without prior dilatation. It was hoped that this technique could replace cholangiography, and the clinical study reported here was commenced. It is disappointing to find that in over half the cases the instrument could not be passed into the common hepatic duct, and thus complete inspection of the biliary tree was not possible. We have, however, shown that the instrument is easy to use and time efficient, and can provide a view of the common bile duct in 84 per cent of cases. A higher success rate would be achieved if cystic duct dilatation was employed in cases of failed cannulation, but this would be time consuming. We had no negative explorations of the common bile duct and this is directly attributed to the use of this instrument.

The instrument costs of the order of £2000 for the permanent eyepiece and attachments. The disposable endoscopic elements cost £120 each and can be used about six times each. As length of hospital stay is increased to an average of 15 days[1] after common bile duct exploration, even if only a small number of people benefit from the use of the endoscope the instrument has the potential to pay for itself in a very short time.

We are sure that this instrument is useful in clarifying cholangiographic abnormalities of the distal biliary tree. Little is added to the operation when using the instrument and we are confident that it has the potential to reduce the rate of negative exploration of the common bile duct.

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Rebound tenderness test

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The usefulness of the rebound tenderness test in indicating peritonitis was prospectively assessed in 142 unselected patients admitted as emergencies with abdominal pain and tenderness. It was found to be of no predictive value.

The rebound tenderness test (RTT) is authoritatively advocated[1,2] and, from personal observation, generally and credulously practised in the diagnosis of acute abdominal pain It is performed by gradually increasing the pressure of the palpating hand over the tender spot, and then suddenly removing it. A start of pain makes the test positive, and this is generally held to indicate the strong likelihood of peritonitis.

However, it may be argued that, as tenderness is simply the sensory perception of irritated nerve endings stimulated by a change in tissue tension through distortion, a rapid alteration will be more unpleasant than a slow one. If this is so, rebound tenderness may signify nothing more than simple tenderness; and tenderness to abdominal palpation has other causes besides peritonitis.

The test, theoretically at least, is therefore of doubtful value, and Prout[3] has already shown its limitations. Although rebound tenderness is still widely sought, if meaningless, it must inflict much fruitless discomfort; it may also be diagnostically misleading.

Methods

One hundred and fifty unselected, though not consecutive, patients, comprising 63 males and 87 females (age range 7–84 years, mean 37, median 46) admitted over 20 weeks during the duty hours of one surgical firm were examined by one of us (ML). The initial RTT result was recorded in each case. Equivocal results were regarded as negative in order to err, if anything, in favour of specificity. When clinically indicated physical signs were reassessed at intervals, but this was not part of the study. The final diagnosis was recorded when it became available.

Results

Eight of the 150 patients had no abdominal tenderness at all and were excluded from further study (two hepatic metastases and one each of abdominal aortic aneurysm, gastroenteritis, pneumonia, myocardial infarction, disseminated prostatic carcinoma and gastric carcinoma). Of the remaining 142, 88 had a positive and 54 a negative RTT (19 patients with equivocal tests were counted as negative). *Table 1* shows how the diagnoses of the 142 patients were related to the RTT and to peritonitis.

The results shown in *Table 2* suggest that while the RTT had a reasonably good sensitivity (43 out of 53 cases of peritonitis were correctly anticipated, sensitivity 0·81) it had a low specificity (the test was also positive in 45 of 89 patients in whom there was no evidence of peritonitis, showing specificity of only 0·50). The test had a positive predictive value of only 49 per cent.

The study group included 14 children whose ages ranged from 7 to 16 years. The findings were similar to those of adults: the sign was positive in two with peritonitis but also in six without peritonitis; it was negative in two with peritonitis and negative in four without.

Discussion

Abdominal tenderness can be found in conditions as diverse as ureteric colic and diverticulitis, perforated ulcer and pelvic inflammatory disease: by itself it does not indicate peritonitis. The question is: does the RTT help in discriminating tenderness from peritonitis from tenderness from non-peritonitic causes?

Table 1 *Diagnosis and RTT results in 142 patients with abdominal tenderness*

	Peritonitis	Number	No peritonitis	Number
RTT positive	Appendicitis	21	Non-specific abdominal pain	16
	Cholecystitis	4	Ureteric colic	6
	Diverticulitis	5	Gastroenteritis	6
	Haemoperitoneum	1	Pelvic inflammatory disease	4
	Perforated viscus	12	Biliary colic	2
			Small bowel obstruction	1
			Dyspepsia	1
			Cystitis	1
			Inflammatory bowel disease	8
	Total	43	Total	45
RTT negative	Appendicitis	6	Non-specific abdominal pain	7
	Cholecystitis	2	Gastroenteritis	9
	Perforated viscus	2	Ureteric colic	6
			Biliary colic	5
			Dyspepsia	2
			Cystitis	3
			Pelvic inflammatory disease	2
			Trauma	3
			Small bowel obstruction	2
			Gastrointestinal bleed	2
			Constipation	3
	Total	10	Total	44

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Table 2 *Sensitivity and specificity of the RTT*

	Peritonitis positive	Peritonitis negative
RTT positive	43	45
RTT negative	10	44

This study provides no support for the teaching and practise of the RTT. Indeed the test was found markedly positive in the majority of patients who were finally considered to have non-surgical abdominal pain, patients in whom Carnett's test[4–7] was usually positive, indicating that the source of the pain was in the anterior abdominal wall.

We do not consider these findings to be in conflict with the pioneering work of De Dombal and colleagues in computer-aided diagnosis of the acute abdomen[8], although they list rebound tenderness as 'vital' information. However if the RTT is simply a more dramatic way of demonstrating tenderness and guarding, also listed as 'vital', and so is simply another aspect of what is already being recorded, it is possible that omission of the test from their data collection chart would not change their results.

In conclusion, we agree with Prout[3] that the demonstration of rebound tenderness suffers the twin disadvantages of being unpleasant for the patient and of being diagnostically useless. In 1964 Rex Lawrie said that the test was 'an unkind way of emphasising what is already obvious'[3]; perhaps, 26 years after his condemnation and 20 years after Prout's, it is time the test was abandoned.

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One hundred patients with hepatic metastases from colorectal cancer treated by resection: analysis of prognostic determinants

One hundred patients with hepatic metastases from colorectal cancer underwent 'radical' liver resection from 1980 to 1989. At least 1 cm of normal parenchyma surrounded the tumour and no microscopic invasion of resection margins was evident. The disease was staged according to our own staging system. Lobectomy was performed in 50 patients and non-anatomical resection in the remainder. The postoperative mortality rate was 5 per cent and the major morbidity rate was 11 per cent. The actuarial 5-year survival rate for patients in stages I, II and III was 42 per cent, 34 per cent and 15 per cent respectively ($P<0{\cdot}001$). *The overall actuarial 5-year survival rate was 30 per cent. The prognostic importance of various patient and tumour variables was evaluated by univariate analysis and then by multivariate analysis. Age of patient, site of primary, disease-free interval between treatment of primary and of hepatic metastases, preoperative carcinoembryonic antigen levels, and number of metastases, did not relate to prognosis, while sex* ($P=0{\cdot}024$), *stage of primary* ($P=0{\cdot}026$), *extent of liver involvement* ($P<0{\cdot}001$), *distribution of metastases* ($P=0{\cdot}01$) *and type of surgery* ($P=0{\cdot}028$) *significantly affected prognosis as single factors. Multivariate analysis revealed that only the extent of liver involvement and stage of the primary tumour were independent predictors of survival. We conclude that liver resection is effective in selected patients with hepatic metastases from colorectal cancer. In resectable patients it is not yet possible to formulate a clear prognosis based on clinical factors. The extent of liver involvement and the staging system used may be significant, although not absolute, indicators of outcome.*

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Since Foster and Berman's review in 1977 of hepatic resection for metastatic cancer[1], there has been increasing interest in the surgical treatment of liver metastases, mainly in the context of metastatic colorectal cancer. While confirming the good results obtained, several later studies[2–17] have focussed on the importance of prognostic variables in selecting candidates for safe and effective hepatic resection. However, the results are still conflicting

The aim of the present paper is to elucidate the value of prognostic factors by analysis of 100 consecutive patients treated by one surgical team While this series represents the largest series of radical hepatic resections undertaken for metastatic colorectal cancer reported from a single institution, it includes 48 patients already reported in 1986[12].

Patients and methods

One hundred patients with hepatic metastases from colorectal adenocarcinoma were submitted to radical hepatic resection between May 1980 and February 1989 Surgery was considered radical when no gross residual disease was evident within or outwith the liver, when at least 1 cm of normal hepatic parenchyma surrounded the resected tumour, and when microscopic invasion of resection margins was not detected histologically. Seven patients submitted to non-radical resection during the same period are not considered here.

The characteristics of the patients are shown in *Table 1* Seventy-one patients had metachronous hepatic metastases detected after an average of 23 months (range 3–60 months) from resection of the primary All patients with a preoperative diagnosis of hepatic metastases were evaluated by abdominal ultrasonography, computed tomography (CT), and angiography of the arterial and venous system of the liver

To exclude additional distant metastases and/or local recurrence of the primary tumour, chest X-ray, barium enema, colonoscopy and, in patients previously submitted to abdominoperineal resection, pelvic CT scans were performed. Further instrumental examinations were indicated only on the basis of symptoms or biochemical abnormalities Routine biochemical studies included hepatic enzyme serum levels and carcinoembryonic antigen (CEA) determinations

The extent of liver involvement and the site and number of metastases were assessed by CT scanning, ultrasonography and intraoperative examination, and in recent years by intraoperative ultrasonography

In patients with synchronous metastases not detected preoperatively, the characteristics of metastases were assessed intraoperatively by inspection and, in a limited number of patients, by intraoperative ultrasonography.

The distribution of the series according to our own staging classification[18] is reported in *Table 2*. It is noteworthy that only 42 per cent of the patients had a single metastasis involving less than 25 per cent of the hepatic parenchyma (stage I), while 31 per cent were allocated to stage II and 27 per cent to stage III The surgical procedures performed are shown in *Table 3* 'Metastasectomy' was not performed and the choice of the surgical procedure was dictated by the extent of liver disease Fifty of the patients underwent formal or extended lobectomy and the others had non-anatomical resections Wedge resections (included as non-anatomical resections) were performed when the liver metastasis was marginal or situated in the residual lobe (bilateral metastases) Intestinal resection was undertaken at the time of hepatic surgery in 13 patients, four of whom had local recurrence

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Table 1 *Characteristics of the series*

	No. of patients	Median age (range)
Sex		
Male	62	
Female	38	
Age		57 years (28–74 years)
Site of primary		
Colon (excluding sigmoid colon)	37	
Sigmoid colon	35	
Rectum	28	
Stage of primary		
Dukes' B	32	
Dukes' C	52	
Undefined	16	
Disease-free interval		
Synchronous	29	
Metachronous	71	
Preoperative carcinoembryonic antigen*		
≤50 ng/ml	45	
>50 ng/ml	43	
Not measured	12	
Extent of liver involvement		
H_1 (≤25%)	61	
H_2 (25–50%)	29	
H_3 (>50%)	10	
Number of metastases		
1	58	
2–3	24	
>3	9	
Undefined	9	
Distribution of metastases		
Single	58	
Multiple unilobar	28	
Multiple bilobar	14	
Type of surgery		
Non-anatomical resection	50	
Lobectomy	50	

* Before hepatic resection

Table 2 *Degree of liver involvement*

	Number of metastases			
Liver involvement	Single	Multiple	Bilateral	Total
H_1 ≤25%	42	12	7	61
H_2 25–50%	12	13	4	29
H_3 >50%	4	3	3	10
Total	58	28	14	100

Table 3 *Surgical procedures*

Extended right lobectomy	7
Right lobectomy	37
Left lobectomy	6
Left lateral lobectomy	11
Non-anatomical resection	39

Follow-up consisted of physical examination, CEA determinations, liver function tests and abdominal ultrasonography every 2–3 months (depending on patient accessibility). In the absence of suspected relapse, chest radiography, abdominal CT scan, and colonoscopy were performed at 6 monthly intervals. The median follow-up period was 17 months (range 1–97 months). No patients were lost to follow-up

Statistical methods

Survival and disease-free survival were calculated by the life-table method; comparison of different survival curves were estimated by the log-rank test as described by Peto *et al.*[19] Cut-off values for different parameters were chosen on the median value. Cox's proportional hazards model[20] was used in multivariate analysis to determine the importance of each variable, a step-down procedure for variable selection was used and all variables were entered and then selected in order of statistical significance.

Results

There were no intraoperative deaths. Five patients died in the postoperative period from hepatorenal failure, four after major resections (three right lobectomy and one extended right lobectomy) and one after non-anatomical resection of cirrhotic liver. Non-lethal major complications were observed in 11 patients; such complications were not related to the extent of hepatic resection (five after lobectomy and six after non-anatomical resection). In two patients the complication was related to synchronous resection of primary colorectal cancer (one anastomotic leak and one pancreatic fistula afer extended resection). Minor complications (pneumonia, pleural effusion, transient ascites, jaundice) were observed in 28 patients (*Table 4*).

Median estimated operative blood loss was 900 ml; being 1200 ml (range 0–4100 ml) and 600 ml (range 0–2700 ml) respectively following lobectomy and non-anatomical resection.

Median postoperative stay in hospital was 15 days (range 5–74 days).

Survival

The overall 5-year actuarial survival rate was 30 per cent and the 5-year actuarial disease-free survival rate was 11 per cent (*Figure 1*). The actuarial 5-year survival rate was 42 per cent, 34 per cent and 15 per cent for stage I, stage II and stage III respectively; no significant difference between stages I and II was detected while both curves were significantly different from that of stage III ($P<0.001$).

Univariate analysis

Among the considered factors, age of patient, site of primary, disease-free interval between treatment of primary and of hepatic metastases, preoperative CEA levels, single *versus* multiple liver metastases and number of metastases were not significantly related to prognosis. On the other hand, sex, stage of primary, extent of liver involvement, distribution of multiple

Table 4 *Postoperative complications*

Type of complication	No.
Lethal complications	
Haemorrhage	1
Hepatic failure	1
Renal failure	1
Myocardial infarction	1
Ischaemic colitis	1
Total	5 (5)
Non-lethal complications	
Subphrenic abscess	5
Biliary fistula	3
Haemorrhage	2
Abscess + biliary leakage	1
Pancreatic fistula	1
Anastomotic leakage	1
Total	13 (13)
Minor complications	
Pneumonia	22
Transient jaundice and ascites	2
Pneumothorax	1
Urinary infection	1
Total	26 (26)

Values in parentheses are percentages

metastases and type of surgery, had significant prognostic importance (*Table 5*).

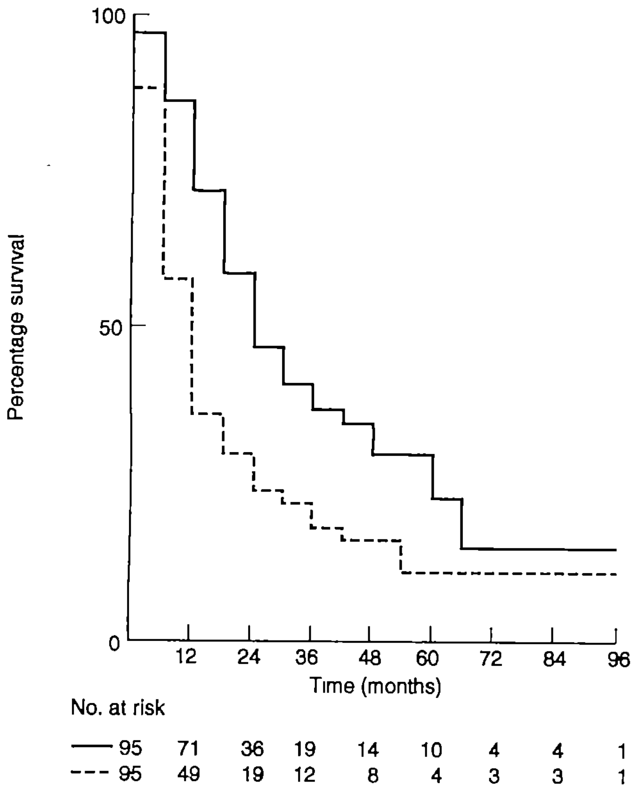

Figure 1 *Actuarial overall survival and disease-free survival of 95 patients resected for hepatic colorectal metastases* ——, *Overall*, ---, *disease-free*

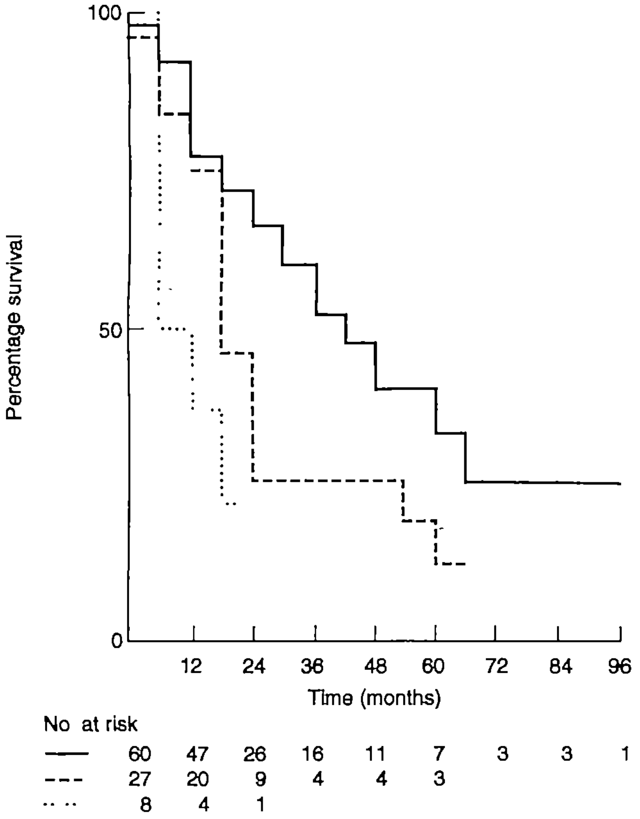

Figure 2 *Actuarial survival by extent of liver involvement* (*see* Table 1). *Difference among the curves was significant* (P<*0·001*)

Table 5 *Survival by prognostic factors*

Prognostic factor	No. of patients	Median survival (months)	Median disease-free survival (months)	5-year survival (%)
Sex				
Male	57	25	14	23
Female	38	49	17	40
Age				
≤57 years	53	26	12	23
>57 years	42	33	13	28
Site of primary				
Rectum	27	25	11	13
Colon	68	30	14	19
Stage of primary				
Dukes' B	29	43	20	47
Dukes' C	50	27	15	24
Undefined	16	16	7	17
Disease-free interval				
Synchronous	28	24	16	31
Metachronous	67	29	15	28
Preoperative carcinoembryonic antigen level				
≤50 ng/ml	44	39	17	27
>50 ng/ml	39	24	14	25
Extent of involvement				
H_1	60	44	17	40
H_2	27	22	11	19
H_3	8	12	9	–
Number of metastases				
1	58	36	18	38
2–3	22	26	17	–
>3	7	28	27	40
Undefined	8	18	18	–
Distribution of metastases				
Single	58	36	18	38
Multiple	37	24	19	16
Unilobar	26	21	9	–
Bilobar	11	63	24	53
Type of resection				
Lobectomy	46	24	11	12
Non-anatomical	49	36	15	21
Overall	95	28	15	30

Five patients dying in the postoperative period after hepatic resection are excluded from this analysis

As a single factor the extent of liver involvement emerged as the most important parameter (*Figure 2*). The 5-year survival rate of patients with H_1, H_2 and H_3 disease (see *Table 1*) was respectively 40 per cent, 19 per cent and 0 per cent ($P<0{\cdot}001$). Patients with Dukes' B primary tumours did significantly better ($P=0{\cdot}024$) than those with Dukes' C and Dukes' undefined tumours (all operated on elsewhere) The 5-year actuarial survival rate of females was 40 per cent *versus* 23 per cent in males ($P=0{\cdot}026$).

While no difference was evident between the outcome in patients with single and multiple metastases, the survival rate of patients with bilobar metastases was higher ($P=0{\cdot}01$) than that of patients with multiple unilobar metastases.

Patients who underwent non-anatomical resection had a better prognosis than those treated by lobectomy ($P=0{\cdot}028$) but as the extent of resection was generally related to the extent of liver disease, patients submitted to non-anatomical resection had less liver involvement.

Multivariate analysis

Multivariate analysis revealed that only two factors were independently related to survival (*Table 6*), namely the extent of liver involvement and the extent of the primary colorectal tumour as classified according to the Dukes' system

Recurrence

Relapse was detected in 69 patients after a median actuarial disease-free period of 17 months (range 2–58 months). The first site of relapse was the liver alone in 28 patients (41 per cent), extra-abdominal sites in 19 (28 per cent), intra-abdominal

Table 6 *Multivariate analysis*

Variables	Relative risk	Degrees of freedom	χ^2	Probability (P)
Liver involvement				
H_1	1	2	14·02	<0·001
H_2	2·39			
H_3	2·61			
Dukes' stage				
B	1	2	6·9	0·03
C	2·89			
Undefined	2·14			
Sex				
Female	1	1	2·9	0·09
Male	1·751			
No. of metastases				
Single	1	1	0·06	0·8
Multiple	1·084			
Type of surgery				
Non-anatomical resection	1	1	0·01	0·9
Lobectomy	1·055			

extrahepatic organs in nine (13 per cent) and the liver plus other organs in 13 (19 per cent). Therefore, 60 per cent of relapsing patients had liver involvement as part of their initial recurrence If both initial and later sites of recurrence are considered, the hepatic recurrence rate was 38 per cent, the extra-abdominal rate 20 per cent, the intra-abdominal extrahepatic rate 13 per cent, and the hepatic plus other organs recurrence rate 29 per cent.

The 5-year projected analysis suggests that 40 per cent of all patients resected have not developed recurrence in the liver.

An analysis was also made to define factors which could indicate the risk of hepatic or distant recurrence. It was found that the risk of extrahepatic metastases alone was significantly related to the extent of liver involvement. Five-year actuarial relapse rates were 60, 81 and 100 per cent in H_1, H_2 and H_3 patients respectively ($P=0·01$). No factor emerged as a significant indicator of hepatic relapse.

Of the four patients who underwent synchronous hepatic and intestinal resection for local recurrence, one had hepatic relapse and two extra-abdominal relapse. All seven patients who underwent non-radical resection had a recurrence within 1 year.

Discussion

The results observed in 100 patients submitted to radical hepatic resection for metastases from colorectal cancer lend further support to the value of surgery as a means of treating this disease when metastasis is confined to the liver. Data from reported series (the present series included) indicate that 5-year actuarial survival rates range from 23 per cent[21] to 40 per cent[9], that operative mortality ranges from 0[9,10,16] to 14 per cent[22] and morbidity rates range between 11 (present series) and 46 per cent[16].

The long term results of hepatic resection can be compared with the survival of untreated patients and with the results observed after other treatments such as locoregional and systemic chemotherapy. The Registry of Hepatic Metastases[15] reported that from literature review, the median survival of 921 untreated patients with potentially resectable hepatic metastases ranged from 6 to 24 months and that there were only 11 5-year survivors, seven of whom did not have histologically proven liver metastases.

The overall actuarial median survival of our surgical patients was 28 months; the corresponding survival of a consecutive series of 48 patients treated with intra-arterial fluorodeoxyuridine was 12 months[23]. Comparing stage by stage, median actuarial survival of stage II patients treated by surgery and chemotherapy was 45 and 20 months respectively, while median survival of stage III patients was 19 and 12 months respectively[23]. The results of systemic chemotherapy are no better than those reported after intra-arterial chemotherapy[24], and it must be assumed that, when applicable, surgery still achieves the best results at an acceptable cost.

We consider that the major remaining problem is not to demonstrate the value of surgical treatment of hepatic metastases, but to define a consistent set of indications for resection. Data from the literature are conflicting in this regard as institutional series are often small, heterogeneous and analysed in different ways. Hughes *et al.* have reported data derived from a collected series of 859 patients included in the Registry of Hepatic Metastases[15], and their results will be compared with those of the present study wherever possible. Among the factors frequently evaluated, the following are not useful prognostically: site of the primary tumour[6,13,16,25], pre-resection CEA level[6,10] and type of hepatic resection[6,10,11,16,22]. The specific influence on survival of other factors is controversial. A trend in favour of females was observed in some studies[16,26,27] as well as our own, but our multivariate analysis showed that this factor did not retain prognostic significance. Stehlin *et al.*[27] reported that age was a significant predictor of long term mortality, but this has not been confirmed by our own and other studies[6,9,15]. The stage of primary colorectal tumour was, in our analysis, the second strongest prognostic indicator. Adson *et al.*[26] consider that the extent of primary lesion was the major determinant of survival, an opinion shared by some[6,15,25,28], but denied by others[9–11,14,16,21,27,29].

Most authors do not consider that the disease-free interval between the treatment of the primary and of the hepatic metastases is prognostically important, but Hughes *et al.*[15] reported that the survival rate of patients with an interval of longer than 1 year was significantly higher than that of patients with a shorter disease-free period. Logan *et al.*[30] observed that patients with a delay of more than 2 years before the detection of hepatic metastases had a median survival time of 40·5 months as opposed to 23·3 months in those with synchronous metastases.

The extent of liver involvement appeared to be the most important determinant of survival in our study. Ekberg *et al.*[11] also found a significant correlation with survival, but such significance was not confirmed by others[16,27]. To our knowledge, no other author has considered percentage involvement of the liver as a prognostic factor. However, an approximate evaluation of the mass of the hepatic neoplasia has been reported by several authors with conflicting results. In some studies[15,21,26] patients with a small solitary metastasis did slightly better than patients with a large one, while in others[9,14,16,25,28] the size of the metastases was not prognostically influential. Moreover, Adson *et al.*[26] suggested that patients with small multiple metastases do worse than those with large multiple ones.

Some authors[10,11,27] have observed that patients with less than four metastases have improved survival in comparison with those having four or more Hughes *et al.*[15] reported that the 5-year survival rate of patients with a single metastasis was significantly better than that of patients with multiple metastases and that a worsening trend was evident with increasing number of liver metastases. This contention has been denied by others[6,14,16,22,25,26,28] and by the results of the present study.

Several studies[11,15,16,25,27] have shown that the lobar distribution of metastases (i.e. unilobar *versus* bilobar) did not relate to prognosis. In our study the patients with bilobar metastases had a higher 5-year survival rate than patients with unilobar metastases ($P=0·01$) although this difference was not confirmed on multivariate analysis. Thus, patients with resectable bilobar metastases did at least as well as those with unilobar disease, not worse as reported by August *et al.*[10].

As in our own experience, others[31,32] have observed higher survival rates after 'partial lobectomy' than after more extensive resection. A number of authors[9,11,16] have reported that the extent of resection was not a significant determinant of survival and that the number of metastases was important rather than the amount of liver removed. Our multivariate analysis supports the contention that the extent of resection does not influence prognosis given that it is correlated with the extent of liver replacement.

A positive histological resection margin or clearance of less than 1–2 cm has been found to be one of the most important determinants of survival[9–11,15,16,32]. Since our study involved only patients with negative histological margins and clearance of more than 1 cm we cannot contribute to this debate. However, it is noteworthy that all seven patients undergoing non-radical resection developed recurrence within 1 year.

To our knowledge only five other papers have reported a multivariate analysis[6,11,15,16,27] and all found that radical surgery (absence of residual intrahepatic and extrahepatic disease, negative margins of resection) was one of the most important prognostic factors. Other identified factors were stage of primary tumour[6,15], stage of hepatic metastases[16], number of metastases[11,15], maximum size of the lesion (more than 8 cm) and disease-free interval before hepatic resection[15].

We feel that patients cannot yet be selected for liver surgery on the basis of the factors considered since none of them (except non-radical surgery) can be regarded as absolute contraindications to resection. We consider that every patient with hepatic metastases confined to the liver should be evaluated as a candidate for resection, and it should be remembered that patients with limited hepatic replacement (i.e. less than 25 per cent) and a Dukes' B primary tumour have a significantly higher probability of 5-year survival than patients with extended hepatic replacement (more than 50 per cent) and a Dukes' C primary tumour. The latter patients are candidates for resection only if surgery carries an acceptably low risk of mortality and morbidity. The results of the present study and that of Holm *et al.*[16] suggest that hepatic resection can produce worthwhile results in stage I and stage II patients where 5-year survival rates of 42 and 34 per cent respectively can be achieved. Even some stage III patients can benefit in that two of our 23 stage III patients survived for more than 3 years.

The patterns of recurrence after hepatic resection show that about 90 per cent of patients relapse within 5 years (the majority within 3 years) and that in 60 per cent of resected patients, recurrent disease affects the liver, alone or in combination with other sites[6,16,32–34]. Such figures reflect our inability to stage the tumour accurately and reflect the limitations of local treatment for what is probably a disseminated metastatic disease.

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Controlled hepatic bipartition for transplantation in children

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In recent years the number of liver transplants being carried out has increased dramatically, resulting in a shortage of livers from heart-beating cadaver donors. The shortage is particularly critical for paediatric recipients, and led in the early 1980s to the concept of reduced-size grafts from older donors for transplantation in children[1]. Recently, technical improvements have reinforced the validity of this concept[2-4]. It has been demonstrated by ourselves and others[5-7] that this technique dramatically reduces the mortality rate among children on the waiting list, without major detrimental effects after transplantation. However, the technique does not increase the number of grafts available for transplantation as the excess liver is destroyed.

One option for increasing the number of available grafts is anatomical and functional division of the liver. Pichlmayr and colleagues[8] were the first to perform and report the transplantation of a single liver into two recipients. A few other cases have been reported[9-11], as well as cases in which bipartition of the liver was performed in the living donor[11-13]. The purpose of this report is to demonstrate the importance of an anatomical assessment of the graft before *ex vivo* hepatic bipartition for transplantation. This method of assessment has not previously been described.

Case report

On 26 March 1990 a liver graft from a 22-year-old donor, blood group O and weighing 70 kg, was offered to our centre for transplantation into a 3-year-old, blood group O girl (patient 1) with biliary atresia.

Patient 1

Previously this girl had had a Kasai operation at the age of 3 months, followed by recurrence of cholestasis and cholangitis. At the time of transplantation, clinical examination revealed a good nutritional status, mild icterus, pruritus, no ascites and no encephalopathy. Body-weight was 13 kg. Liver function tests were as follows: total bilirubin, 45 μmol/l (normal <17); alkaline phosphatase, 941 U/l (normal <90); gamma glutamyl transpeptidase (gamma GT), 296 mU/ml (normal <30); alanine aminotransferase (ALAT), 251 mU/ml (normal <25); aspartate aminotransferase (ASAT), 170 mU/ml (normal <30); prothrombin time, 93 per cent of control. Several oesophageal varices were seen at endoscopic examination. The portal vein was patent with a hepatopetal blood flow on Doppler ultrasound examination. Cardiac, pulmonary and renal function were normal. No extrahepatic infectious site was found.

Patient 2

At the same time a 13-year-old boy, blood group O and weighing 33 kg with Byler disease, presented with a rapid deterioration of liver function. His initial symptoms had occurred at the age of 15 months when pruritus developed. A liver biopsy led to the diagnosis of Byler disease at the age of 5 years. At this time cholestasis was the main clinical problem. Pruritus was controlled with cholestyramine. The situation remained stable until December 1989 at which time clinical examination showed jaundice and a liver decreased in size. Liver function tests revealed hyperbilirubinaemia and severe liver insufficiency with a prothrombin rate at 40 per cent of control. Liver transplantation was indicated and pretransplant assessment was done in January 1990; nutritional status was good and no ascites or encephalopathy was found. Liver function tests showed a rise of serum ASAT (779 mU/ml) and ALAT (600 mU/ml), serum alkaline phosphatase was 538 mU/ml and total bilirubin was 167 μmol/l. The prothrombin rate was at 42 per cent of control. Blood tests for viral hepatitis type A and B were negative. At Doppler ultrasound examination the portal vein was patent; its diameter was measured at 13 mm. No cardiac, pulmonary or renal disease or infectious site was found. At the beginning of March 1990 his liver function deteriorated and he developed mild encephalopathy, ascites and lower limb oedema. Bilirubin increased to 288 μmol/l and decreased albumin and a prothrombin rate at 24 per cent of control suggested the need for urgent liver transplantation.

It was decided to transplant both patients after *ex vivo* bipartition of the graft.

Operative procedure on the graft

The graft was obtained from a heart-beating cadaver and preserved in University of Wisconsin (UW) solution. The right portal vein was not missing and no hepatic artery was found to the right of the common hepatic duct or arising from the left gastric artery. After cholecystectomy, a cannula was inserted into the common bile duct and a second one into the common hepatic artery. Rapidly, the graft was taken out of its bowl, its diaphragmatic surface was placed on a film plate and two liver radiographs were taken after injection of 2 ml amidotrizoate contrast medium (Radioselectan®, Schering, France) at 4°C into the artery and the biliary tree, successively. Immediately afterwards the cannulae were removed and the biliary and arterial trees were abundantly washed out with cold UW solution.

The left graft was given to patient 1 and the right graft to patient 2. In this report, anatomical divisions are those described by Couinaud[14,15]. Because of the small size of patient 1 compared with the left liver transplant, the graft was reduced by resecting segment IV.

The parenchyma was transected posteriorly to the right of the round ligament. The elements for segment IV arising from the right part of the umbilical plate were ligated in an extrafascial manner and divided. The parenchyma was then divided posteriorly along the main portal fissure just to the left of the middle hepatic vein. At the posterior part of this transection plane the middle hepatic vein was divided just before it joined the left hepatic vein. Segment I was then resected. Examination of the biliary and arterial radiographs (*Figures 1* and *2*) showed a single right and left bile duct, a single right hepatic artery, but

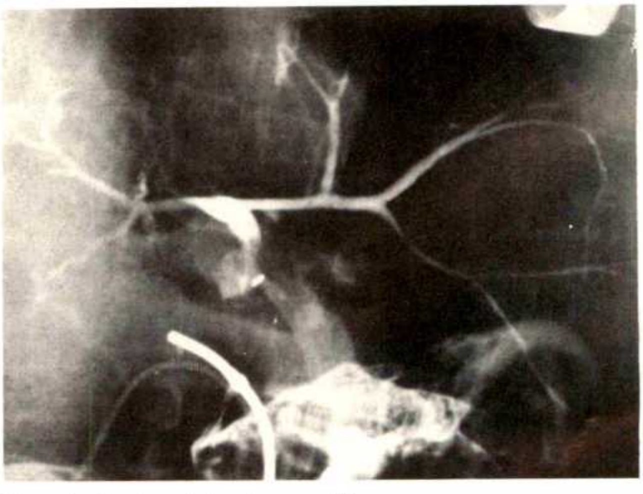

Figure 1 Ex vivo *cholangiogram of liver*

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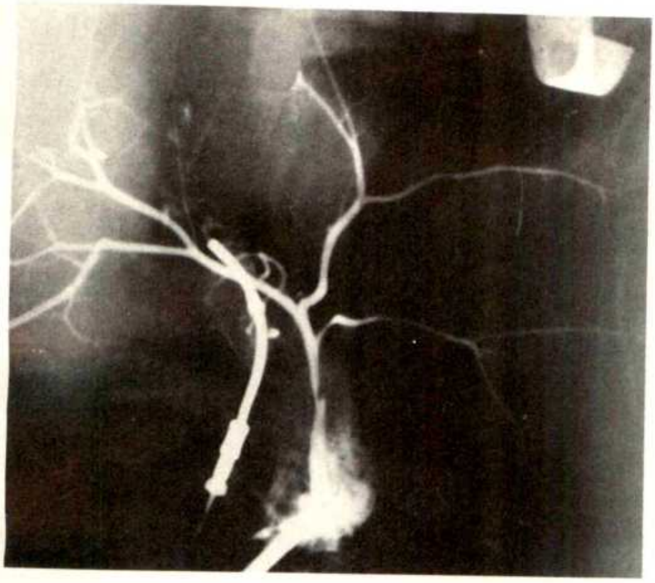

Figure 2 Ex vivo *arteriogram of liver*

duplication of the left hepatic artery with the first branch going to segment II and a second branch going to segments III and IV. For this reason the main hepatic artery was left with the left graft. After introducing a smooth probe into the common hepatic duct the right branch of the hepatic artery was dissected just to the left of the common bile duct and divided. Its proximal end was sutured.

The left hepatic duct was divided without dissection a few millimetres distal to the bifurcation. The right portal vein was divided just after its origin to allow the maximum length of portal vein to go with the left graft; 10 ml of biological glue (Biocol®, Biotransfusion, France) were applied on each transected area. The whole bench procedure including anatomical assessment and bipartition took 1·5 h.

Operative procedure in patient 1

In patient 1 the diseased liver was removed, leaving the inferior vena cava. The graft consisting of the left lobe (segments II and III) was implanted by anastomosing the left hepatic vein of the graft to the orifice joining the three hepatic veins of the recipient. Then, end-to-end anastomoses were made between donor and recipient hepatic artery and portal vein. Revascularization of the graft occurred after 7 h 40 min of cold ischaemia. Biliary reconstruction was done using the Roux-en-Y loop constructed during the Kasai operation.

Operative procedure in patient 2

In patient 2 anaesthesia was induced after complete revascularization of the graft in the first recipient. After total hepatectomy of the diseased liver the right liver graft was orthotopically transplanted. End-to-end anastomoses were done between the right hepatic artery and portal vein of the graft, and the proper hepatic artery and portal vein of the recipient, respectively. No venovenous bypass was used. After revascularization, mild but persisting congestion of segment V was noted. Cold ischaemia time for the graft was 14 h 30 min. Biliary reconstruction was done by anastomosing the common hepatic duct of the graft to a Roux-en-Y jejunal loop.

Results

For patient 1 the intraoperative blood transfusion was 400 ml. Initial progress after operation was good, peak serum ALAT and ASAT levels reaching 679 U/l and 311 U/l at day 1 respectively, and coagulation factor V reaching 50 per cent of control at day 2. At day 3, without clinical or biological signs of deterioration, daily monitoring showed a sudden disappearance of the hepatic arterial Doppler signal. Haematocrit was 40 per cent. Emergency angiography showed occlusion of the hepatic artery. The child was reoperated on urgently; through the recipient's gastroduodenal artery a short clot was removed from the hepatic artery of the graft which was then infused with 50 000 U/ml urokinase for 30 min. Revision of the hepatic artery anastomosis showed neither stenosis nor kinking. Intraoperative arteriography confirmed patency of the branch of segment II as well as that of segment III (*Figure 3*) Further daily monitoring showed an intrahepatic arterial signal. At 6 weeks after transplantation the child was discharged home in good condition with normal liver tests and a positive hepatic arterial Doppler signal in the graft. Heparin treatment started after reoperation was stopped at that time.

For patient 2, 2200 ml red cells were transfused during the operation. Initially there was a peak serum ASAT level of 768 U/l and a rapid improvement of coagulation tests, factor V reaching 41 per cent of control at day 1. Heparin treatment was given until discharge. The subsequent postoperative period was uneventful and the child was discharged home 24 days after transplantation.

Both patients are alive with normal liver function tests 12 months after transplantation.

Discussion

This is a report of a successful *ex vivo* bipartition of a liver for transplantation in two children. Until now only a few cases of *ex vivo* bipartition of the liver (also called split transplantation) have been reported. Most of them were done for patients requiring emergency transplantation[9–11] and a successful outcome in two recipients has been reported only by the group from Chicago[11]. However, even these authors underlined both the rather poor results obtained with this technique compared with those using the standard techniques of whole or reduced-size liver transplantation, and the surgical complications apparently related to the partition of the graft.

An extensive study of liver anatomy[14,15] has shown variations in the shape and size of the liver and its venous, arterial and biliary structures. Although most of these may be ignored for liver resections, this is not so in the context of bipartition for transplantation which requires each graft to be an adequate size and to have normal vascular and biliary structures. The anatomical limitations to *in vivo* or *ex vivo* bipartition or tripartition of a human liver for transplantation have been extensively investigated recently; *ex vivo* bipartition appears impossible in approximately 5 per cent of cases[16]. In the other cases bipartition is feasible provided suitable measures are taken to cope with the anatomical situation.

The present case illustrates one of these anatomical drawbacks. Whereas the venous and biliary structures occurred in the usual manner, there were two important arterial

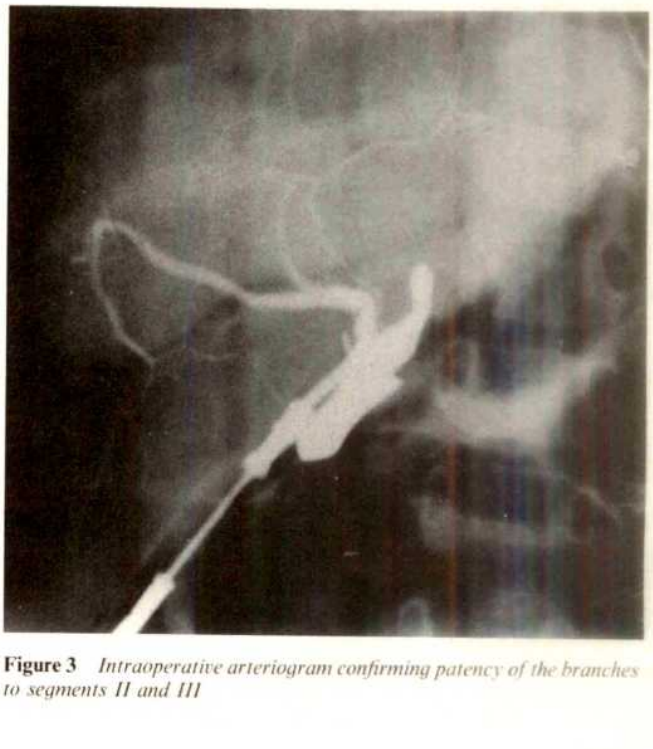

Figure 3 *Intraoperative arteriogram confirming patency of the branches to segments II and III*

variations: a duplication of the left hepatic artery (which is encountered in approximately 50 per cent of cases)[16], and an unusual intrahepatic distribution of the two left arteries, the first supplying segment II and the second supplying segments III and IV (in 90 per cent of cases of left arterial duplication the first branch supplies segments II and III and the second branch segment IV)[16]. In the present case resection of segment IV, which was necessary due to the small size of the recipient, could not solve the difficulty created by the distribution of the duplicated left arteries. Attribution of the proper hepatic artery to the left graft was mandatory and this decision was taken following the arteriogram. Due to the triple obliquity of the liver *in situ*[14,15], study of the arterial distribution is easier when the liver is placed on its diaphragmatic surface.

Dissection of the arterial tree without arteriography could have caused devascularization of the biliary wall or injury to the small branch of segment II with subsequent ischaemia of this segment. On the other hand, if arteriography had also detected an arterial duplication on the right (2 per cent of cases)[16], the situation would have been complex, requiring a precarious double arterial anastomosis either on the left or on the right. In fact we would have rejected the bipartition.

Radiological assessment of the graft on the table prolongs the cold ischaemia time. This, however, can be kept to less than 20 min, a prolongation which is minor compared with the time bonus given by the new UW preservation solution. After the anatomical examination the surgeon may be able to compensate for this delay by performing the bipartition more rapidly. There is a theoretical risk from injecting contrast medium into the bile duct and hepatic artery of the graft, but care was taken to inject less than 2 ml since only second and third order branches need be seen. Injection was performed at low pressure, using amidotrizoate at 4°C. It is unlikely that the hepatic artery thrombosis observed after the operation in the recipient of the left graft was due to the arteriogram as no thrombosis was seen at the level of intrahepatic branches. However, the risk remains to be further evaluated and the use of non-ionic contrast media of low osmolality, such as those used for opacification of meningeal spaces[17], might be more appropriate.

This report does not aim at justifying or defining the indications of *ex vivo* liver bipartition for transplantation, but through a successful example of such a transplantation it primarily aims at underlining the importance of a full anatomical, including radiological, evaluation of the graft. Such an evaluation allows an informed decision on whether bipartition is feasible and how it should be done.

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Surgical anatomy of donor extended right trisegmentectomy before orthotopic liver transplantation in children

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Liver transplantation is now accepted as the treatment of choice for children with end stage liver disease. A major constraint has been the shortage of donor organs of appropriate size. The use of reduced size adult organs has partially alleviated this problem but the previous technique employed was limited to a donor:recipient body-weight disparity of not greater than 3:1. Recently a new technique has been described that allows safe transplantation with a donor:recipient weight ratio of greater than 10:1. This should greatly increase the paediatric donor pool. Anatomical landmarks and techniques necessary for donor reduction hepatectomy are described from the dissection of 50 adult cadaveric livers. Variations in all important biliary and vascular structures necessitated adjustments in operative technique.

Paediatric liver transplantation has been expanding rapidly over the last few years and satisfactory results have been reported from many centres. However, despite an increase in public awareness of the need for organ donation there is a scarcity of paediatric donor livers, particularly in smaller patients. In most major centres the mean waiting time for a child accepted for liver transplantation is about 6 months. During this period the clinical condition of many of the children on the waiting list deteriorates and some 25–30 per cent will die[1].

Bismuth and Houssin[2] first described the technique of reducing adult donor livers. This has now been used in several transplant centres. Unfortunately the technique involves keeping the donor vena cava in place and is only useful for donor:recipient body-weight ratios of not greater than 3:1[3]. This has limited the availability of donor livers for the younger and smaller patients. Recently a new technique was described by surgeons from Hannover[4] and Brisbane[5] which allows transplantation with donor:recipient body-weight ratios of greater than 10:1. Only the left lateral segment with its portal triad and hepatic vein is used and the latter is anastomosed to the recipient vena cava which is left *in situ* after hepatectomy.

The preparation of the left lateral hepatic segment requires an accurate knowledge of potential variations in the anatomy of the bile ducts, hepatic artery, portal veins and hepatic veins. The present study has been found necessary despite the existence of some superb anatomical studies of the liver in the published literature[6–8].

Methods and results

Anatomical observations and resection technique

The specimens used in dissection were 50 cadaveric non-diseased organs obtained at post mortem.

When procuring livers for left lateral segment transplant, a standard procedure is employed except that the liver should be taken with as much falciform ligament and ligamentum teres as possible. These are useful later in attaching the transplanted liver to the body wall. The extended right hepatectomy is sometimes performed *in situ* but this delays the removal of other organs. Hence we believe that the procedure should be performed *ex vivo* as a bench procedure.

Transection of the liver should commence from the posteroinferior surface in view of the importance of the portal triad. The inferior vena cava is opened longitudinally and its major orifices noted (*Figure 1*). The middle hepatic vein often joins the left hepatic vein to form a common trunk draining into the inferior vena cava and this was true in 47 (94 per cent) of our dissections (*Table 1*). The retrohepatic vena cava is removed with a generous cuff around this common orifice for later anastomosis to the recipient vena cava (*Figure 2*). The middle hepatic vein lies superficially over the anteroposterior surface of the liver (*Figure 3*) and will be divided at a later stage of the procedure during the transection of the liver parenchyma. It is sectioned at a distance from the left hepatic vein and the opening into the left hepatic vein is oversewn with a continuous 5/0 polypropylene suture.

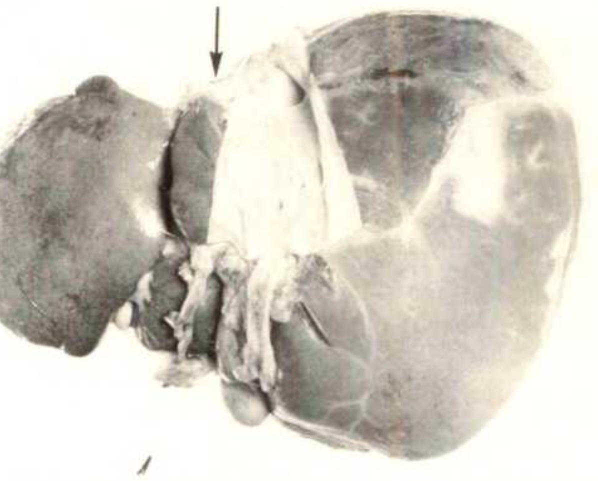

Figure 1 *The retrohepatic inferior vena cava opened longitudinally to display the hepatic venous orifices. (Arrow indicates entry of left hepatic vein)*

Table 1 *Incidence of middle and left hepatic veins joining to form a common trunk*

Authors	Numbers of livers dissected	Number forming a common trunk
Kune[6]	50	49 (98)
Ger[8]	40	36 (90)
Nakamura and Tsuzuki[20]	83	70 (84)
Current report	50	47 (94)

Values in parentheses are percentages

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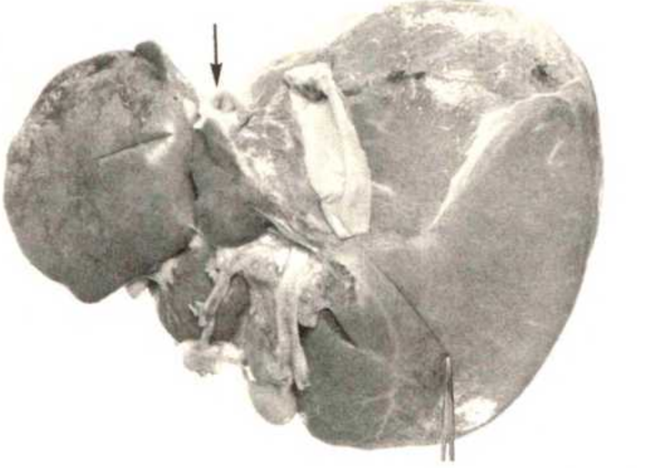

Figure 2 *Most of the retrohepatic inferior vena cava has been removed leaving a cuff around the common orifice of the middle and left hepatic veins (arrowed)*

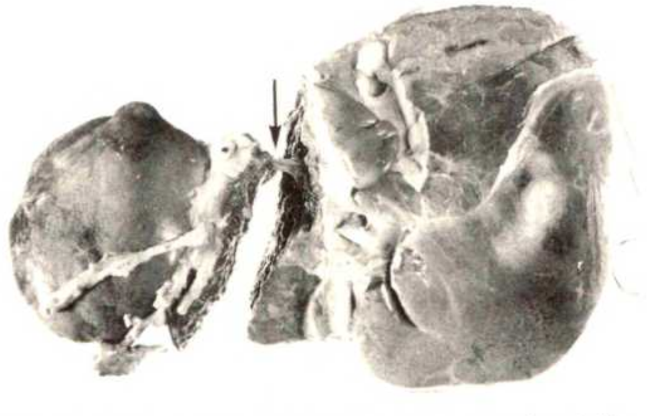

Figure 3 *The liver transected. The middle hepatic vein is shown joining the left hepatic vein before opening through a common orifice into the inferior vena cava (arrowed). Transection of the liver is carried out towards the end of the dissection*

Attention is then turned to the hilum where the valveless portal vein is dissected first, being the most posterior structure. It is also the least variable of all the elements within the portal triad, the left branch in particular tending to be constant in location. There are often two or three branches supplying the hilum and caudate lobe which must be divided between fine ligatures (*Figure 4*). The right branch lies anterior to the caudate process and immediately enters the liver at the right end of the hilar plate, soon dividing into the anterior and posterior branches. The longer left branch lies anterior to the caudate lobe and passes leftward and posteriorly before making a right-angled curve into the liver at the portoumbilical fissure. The portal vein bifurcated in 46 (92 per cent) of the dissected livers; trifurcations or other more complicated arrangements were seen in the remaining four (8 per cent; *Figure 5*) and involved the branch to the right anterior segment (Couinaud segments V and VIII) arising proximally from the main trunk or even from the left branch (*Figure 6*). The right branch should be divided accordingly. Alternatively the right branch, which is about 1 cm in length and shorter than the left, is divided a short distance away from the bifurcation and the defect is closed over with a continuous 6/0 polypropylene suture (*Figure 7*).

The hepatic artery or bile duct is next dissected depending upon which is the more posterior structure. They are very inconstant in their relationship.

Information about the arterial supply of the liver is generally available from the retrieval team. In up to 30 per cent of cases the hepatic artery proper has an abnormal origin, such as from the left gastric or superior mesenteric artery. Less commonly the left hepatic artery itself may arise directly from the coeliac axis or a gastric artery[6]. In the remaining 70 per cent of livers standard anatomy is found with a single hepatic artery arising from the coeliac trunk[9–11]. However, surgical techniques will still have to be adjusted depending upon the variation in the branching pattern of this vessel[12]. The bifurcation of the hepatic artery was always extrahepatic in our dissections and lay proximal to the confluences of the portal veins and bile ducts (*Figure 8*). This arrangement facilitates the division of the right hepatic artery which normally arises from the hepatic artery proper and passes posteriorly to the bile duct. It is important to note that in only about 75 per cent of cases does the hepatic artery enter the liver as two branches (the right and left hepatic arteries). In the remainder the most common pattern is a trifurcation of the hepatic artery with two branches passing to the right side of the liver and one to the left. Any number of branches may be present, however, but as these usually arise outside the liver their identification should not be difficult. However, the frequent arterial anomalies demand that all ligations be performed with the utmost caution.

The cystic artery and duct are next divided between ligatures and the gallbladder removed. The union of the right and left hepatic ducts is always extrahepatic but it is the most superior structure in the hilum and division can be difficult (*Figure 9*). Independent tributaries from the caudate lobe and hilum should be divided between fine ligatures. The right hepatic duct is identified and carefully divided a short distance from the confluence and the defect closed over with 5/0 polydioxanone

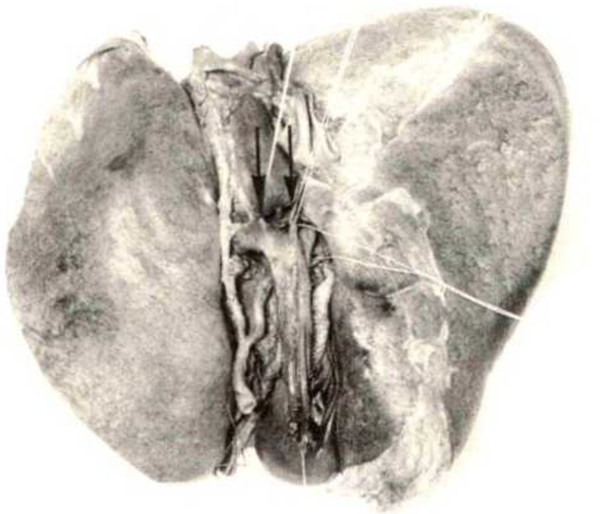

Figure 4 *Branches are shown from the bifurcation of the portal vein supplying the caudate lobe and the hilum of the liver (arrowed). These are divided and the portal vein is mobilized to the left*

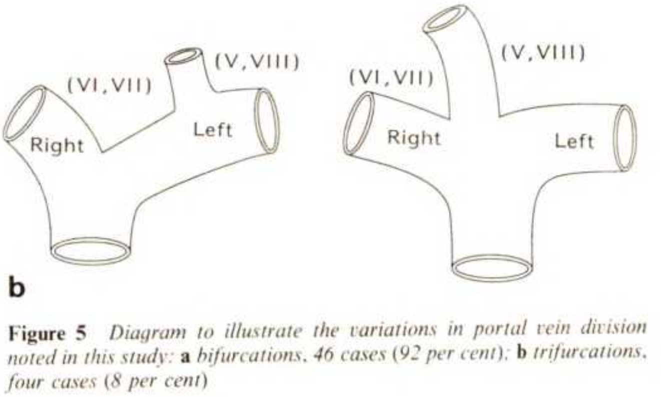

Figure 5 *Diagram to illustrate the variations in portal vein division noted in this study:* **a** *bifurcations, 46 cases (92 per cent);* **b** *trifurcations, four cases (8 per cent)*

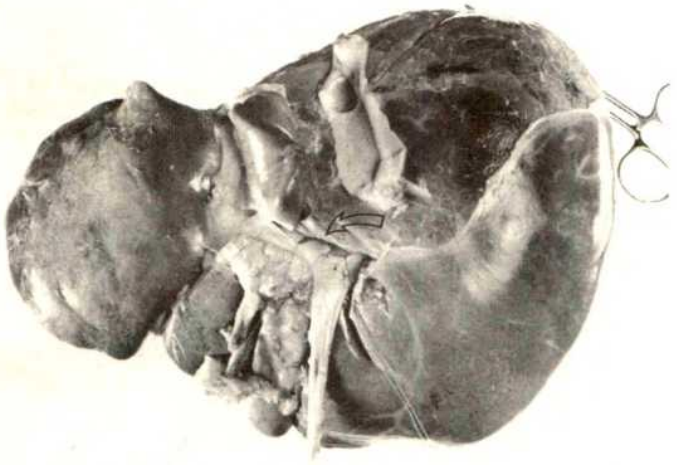

Figure 6 *Trifurcation of the portal vein. The branch to the right anterior segment (arrowed) can be seen coming from the left main branch. A large branch is also noted to the caudate lobe*

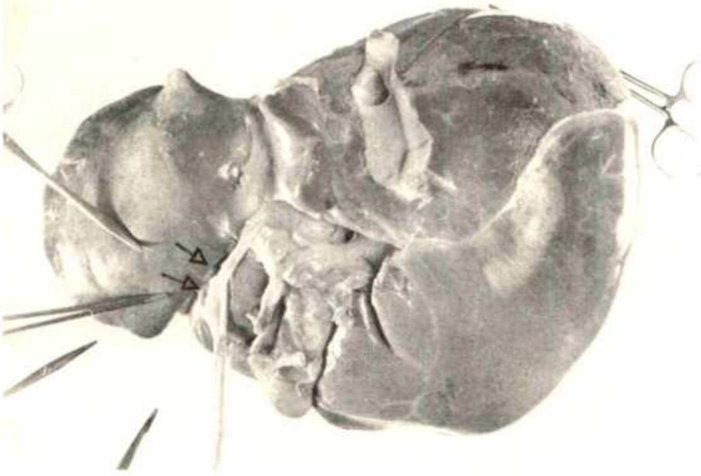

Figure 7 *The portal vein is mobilized to the left. The origin of the divided branches to the right side of the liver has been oversewn (arrowed)*

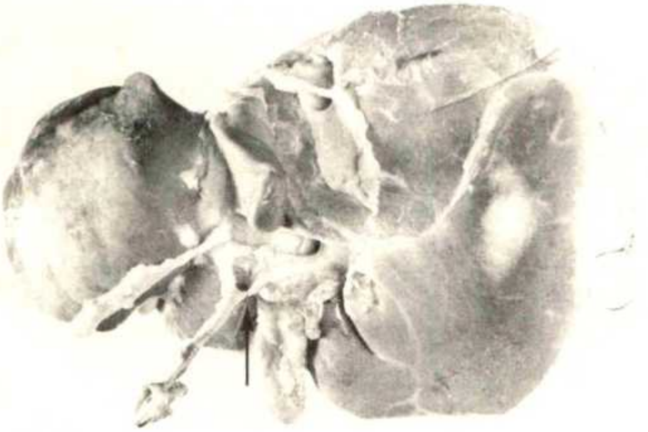

Figure 8 *The extrahepatic bifurcation of the hepatic artery (arrowed)*

sutures. Branches from the right anterior (segments V and VIII) and right posterior (segments VI and VII) segments drained independently into the left duct in 12 (24 per cent) of our dissected livers and with such an arrangement the right branch may sometimes be mistaken for the cystic duct. All the branches must therefore be identified carefully before division.

The surface of the liver is marked for division approximately 2 cm to the right of the portoumbilical fissure (*Figure 10*). This is to avoid the recess of Rex, where the portal triad swings downward and gives branches to the left lateral segment (*Figure 11*). The transection should proceed from the posteroinferior to the anterosuperior surfaces with careful identification and ligation of all biliary and vascular structures. This may be performed with either the ultrasonic dissector or the standard 'Kelly fracture technique'.

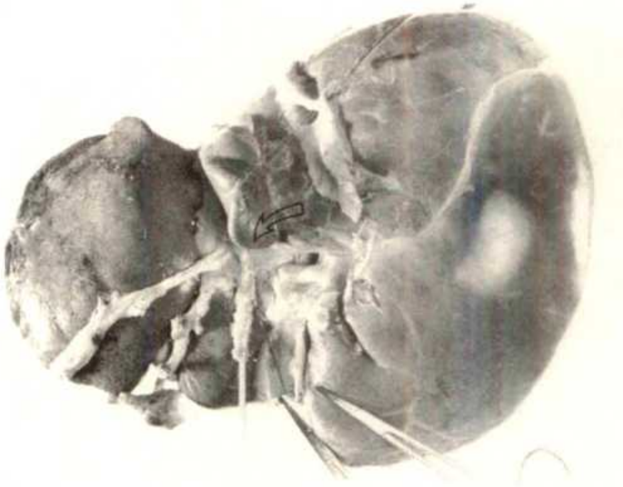

Figure 9 *The right and left hepatic ducts unite in the upper part of the hilum (arrowed) and dissection of the left duct can be difficult. The gallbladder has been removed and the cystic duct has been ligated*

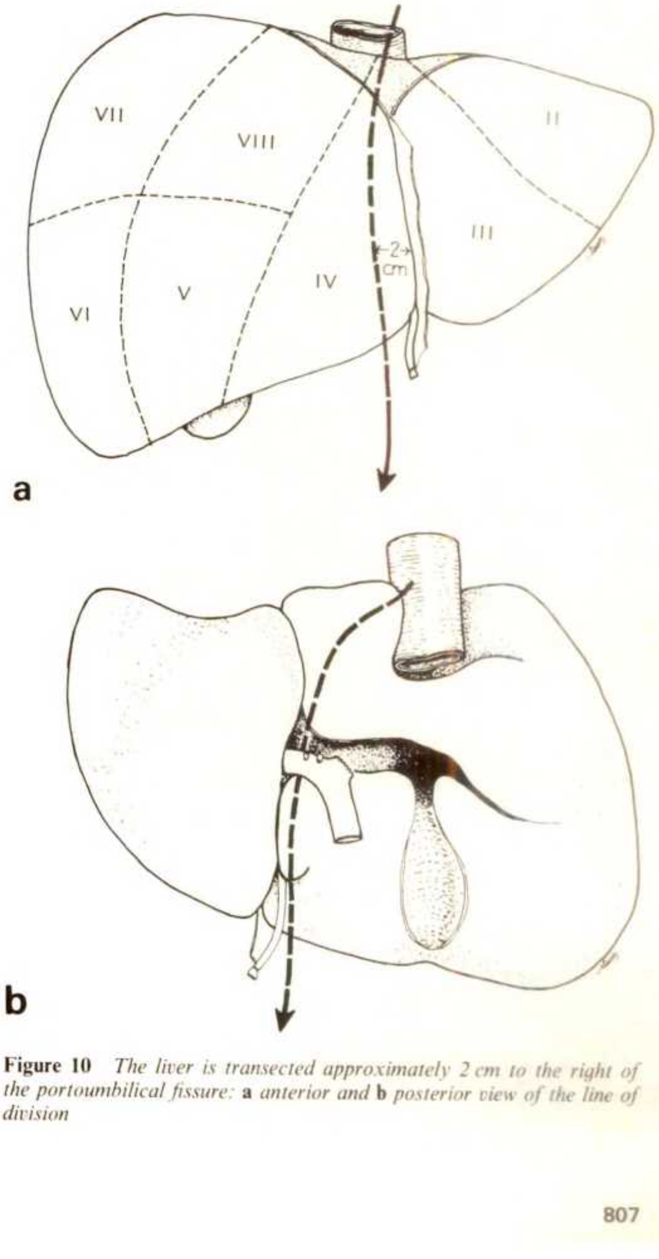

Figure 10 *The liver is transected approximately 2 cm to the right of the portoumbilical fissure:* **a** *anterior and* **b** *posterior view of the line of division*

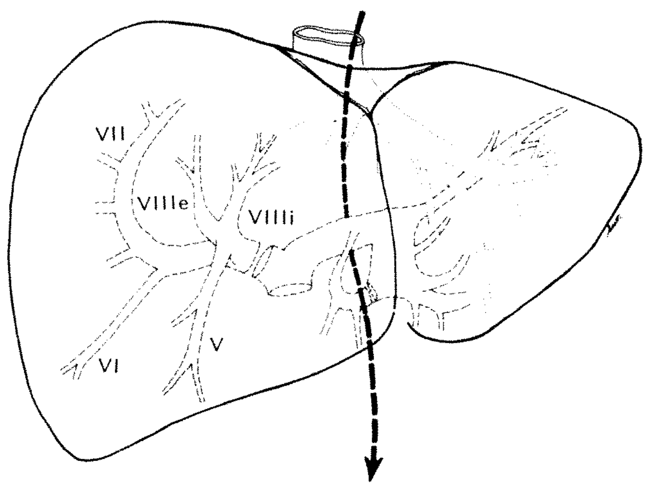

Figure 11 *The liver is divided along a plane that avoids the recess of Rex (broken arrow) in the line of the portoumbilical fissure. It is in this region that branches are given off to the left segment*

The caudate lobe should be routinely removed as its biliary drainage is so variable. The drainage was bilateral in 42 livers (84 per cent) but in six (12 per cent) the drainage was only to the right hepatic system. In addition the caudate lobe has an independent venous drainage into the retrohepatic vena cava. There is a particular risk of infection of a poorly drained caudate lobe in patients receiving immunosuppression.

The transected liver surface is tested for vascular and biliary leakage by perfusion of both the portal structures and hepatic vein. Serious bleeding is most likely to occur from the hepatic venous system as the portal venous and hepatic arterial systems are surrounded by a perivascular fibrous capsule (of Glisson). This capsule protects these structures from injury and makes their identification and ligation easier.

Discussion

Despite the recent increase in the public awareness of the need for organ donation, a significant number of children die while waiting for a suitable organ to become available. The shortage is most severe in the younger age group. Over the last few years the introduction of reduced size adult liver grafts has helped to alleviate this problem and it has been shown that the postoperative results may compare favourably with those of whole liver grafting[13]. However, due to vascular discrepancies and other technical difficulties, the procedure as practised until recently is safe only with a donor: recipient body-weight ratio of not more than 3:1. This has limited the donor pool for very small children.

The use of an isolated donor left lateral segment with its portal triad and hepatic vein[14] and a preserved retrohepatic inferior vena cava in the recipient[15] allows transplantation with a donor:recipient ratio of greater than 10:1. This procedure will markedly increase the donor pool for smaller children.

We believe this procedure is an important addition to the technical armamentarium of liver transplant surgeons. It can save a rapidly deteriorating child when an appropriately sized liver for a conventional transplant is not available. This was confirmed in our own clinical experience where the technique was used in two cases with excellent initial graft function. This is especially so now that livers are being increasingly transplanted in the face of ABO incompatibility[16].

Recently in certain countries where cadaveric liver grafting is not allowed, great interest has been shown in transplanting livers from living relatives. These have mainly involved the left lateral segment[17]. The anatomical landmarks and anomalies described in the current work may be helpful in such technical considerations.

We were able to perform right trisegmentectomy in every case as the right lobe was to be discarded. However, when the right lobe is to be preserved, as in dividing a donor liver for implantation into two recipients of different size or when using a living donor, others have found that it is not possible in 19 per cent of cases[18].

Since the transplant procedure from a living donor can be planned, prolonged preservation of the donor liver is unnecessary. As such, once the hilar structures have been dissected and the left hepatic vein separated, semi-isolated perfusion of the left lateral segment with HTK-Bretschnider solution can be commenced as the liver is being transected. The low potassium content of this solution will allow it to be better tolerated should it enter the circulation of the donor[19].

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Extracorporeal shock wave treatment of common bile duct stones: experience with two different lithotriptors at a single institution

Extracorporeal shock wave lithotripsy (ESWL) is a new treatment modality for retained common bile duct stones. Sixty-two patients (mean age 75 years, range 27–95 years) with retained common bile duct stones were treated with two different lithotriptors. One of the lithotriptors operated on the electrohydraulic principle (Dornier HM-3) ($n=13$*), the other on the electromagnetic principle (Siemens Lithostar®) (*$n=49$*). All HM-3 patients were treated under general anaesthesia, whereas with the Lithostar one patient was treated under general anaesthesia, 43 received analgesia and sedation and five had no analgesia at all. Patients treated with the Lithostar had more sessions (mean 1·9* versus *1·3, *$P<0{\cdot}05$*) and needed more shock waves (mean 8611* versus *2534, *$P<0{\cdot}001$*) than patients treated with the HM-3. Fragmentation was achieved in all patients treated wih the HM-3 and in 42 (86 per cent) patients treated with the Lithostar. In this latter group ten patients underwent common bile duct exploration without complications. Eleven patients had transient haematuria after treatment with the HM-3 and two patients (one in each group) had a subcapsular haematoma of the right kidney, all without clinical sequelae. At follow-up (median· HM-3 43 months, Lithostar 18 months), none of the patients had biliary complaints. We conclude that ESWL of retained common bile duct stones is safe and effective with both lithotriptors and should be considered before surgery in the elderly or high-risk patient.*

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Clinical experience with extracorporeal shock wave lithotripsy (ESWL) for treatment of kidney stones was first reported in 1980[1] ESWL is now the treatment of choice for urolithiasis and more than 500 000 patients with renal stones have been treated worldwide Since these satisfying results in urology, other applications of ESWL have been studied. Sauerbruch *et al* [2] in 1986 reported the successful fragmentation of gallbladder stones and common bile duct stones by ESWL It appeared that stones of different chemical composition could be disintegrated[3,4]. Recently, promising results of ESWL for pancreatic duct stones were reported[5–7] and the effects of high energy shock waves on tumour cells are being studied[8–11]

Common bile duct stones can present as the first sign of gallstone disease or after cholecystectomy with or without exploration of the common bile duct. Surgical common bile duct exploration is an accepted therapy but has serious morbidity and mortality rates in the elderly or high-risk patient[12–14] Several less invasive alternatives for the treatment of common bile duct stones have been developed. Endoscopic sphincterotomy and removal of the stones, with or without mechanical crushing with a Dormia basket, was introduced in 1972 and is nowadays the treatment of choice for elderly patients with common bile duct stones and prior cholecystectomy or for patients with an increased risk for surgery[15–17]. Chemical dissolution with different solvents has been studied, including ethylenediamine tetra-acetic acid (EDTA)[18], mono-octanoin[19,20], methyl-tert-butyl ether (MTBE)[21] or orally administered bile acids[22]. Other alternative invasive treatment methods have also been studied, including intracorporeal shock wave lithotripsy[23–26], laser lithotripsy[27,28], T tube extraction[29,30] and percutaneous transhepatic removal[31], but all these techniques are more cumbersome and less successful than endoscopic removal

In approximately 10 per cent of patients it is not possible to cannulate the sphincter of Oddi and remove stones from the common bile duct[15]. This can be due to discrepancy between the diameter of the stone and that of the distal common bile duct, presence of duodenal diverticulum and previous Billroth II gastric resection or Roux-en-Y anastomosis In these cases, especially in high-risk patients, ESWL offers an attractive alternative to surgical exploration of the common bile duct About 400 patients with common bile duct stones are reported to have been treated with ESWL using either a first- or second-generation lithotriptor[32–35] In this report we present a single institution experience with 62 consecutive patients with retained common bile duct stones using a first-generation electrohydraulic lithotriptor and a second-generation electromagnetic lithotriptor.

Patients and methods

Patients

Inclusion criteria for ESWL treatment in patients with common bile duct stones are summarized in *Table 1*

Patients treated with the Dornier HM-3 lithotriptor Between April 1986 and July 1987, 13 patients (12 women and one man) with mean age 79 years (range 67–92 years) were treated for retained common bile duct stones using the Dornier HM-3 (Dornier Medizintechnik GmbH, Germering, Germany Eleven patients had jaundice and seven had cholangitis Twelve patients had had previous endoscopic sphincterotomy and nasobiliary drainage One patient was treated with percutaneous transhepatic biliary drainage because of a previous

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Table 1 *Inclusion criteria for extracorporeal shock wave lithotripsy (ESWL) of common bile duct stones*

One or more symptoms of obstruction by common bile duct stones (jaundice, abdominal pain, fever)
Endoscopic extraction impossible
Successful positioning of the patient on the lithotriptor and visualization of (at least the most distal) stones by fluoroscopy after contrast injection
No lung tissue, cysts or abdominal aneurysms in the shock wave pathway
No coagulopathy
No pregnancy

Billroth II gastric resection Four patients (31 per cent) had had prior cholecystectomy.

Four patients had solitary stones, four had two stones and five had three or more stones. The diameter of the largest stone ranged from 20 to 52 mm (mean 29 mm). Two patients with common bile duct stones had intrahepatic stones as well

Patients treated with the Siemens Lithostar lithotriptor From September 1987 to November 1990, 49 patients (26 women, 23 men) with mean age 74 years (range 27–95 years) underwent ESWL for common bile duct calculi with the Siemens Lithostar® (Siemens AG, Erlangen, Germany) Seventeen patients suffered from abdominal pain, 19 had jaundice and five had cholangitis Previous endoscopic sphincterotomy and insertion of a nasobiliary tube had been performed in 36 patients. In four patients a Dormia basket had remained impacted in the common bile duct after attempts at endoscopic removal of stones. Nine patients had a T tube *in situ* and four had a percutaneous transhepatic catheter because endoscopy was impossible In 17 patients the gallbladder was still *in situ*. Twenty-two patients (45 per cent) had solitary stones, 13 (27 per cent) had two stones and 14 (28 per cent) had three or more stones The mean diameter of the largest stone was 24 mm (range 10–50 mm). Six patients also had intrahepatic stones. Ten patients had retained stones after cholecystectomy with or without common bile duct exploration

Shock wave treatment

Pretreatment investigations included cholangiography, chest radiography, white blood cell count, serum levels of bilirubin, liver enzymes, amylase and a coagulation profile.

With the HM-3 lithotriptor all patients were treated in the supine position under general anaesthesia with 'high-frequency jet ventilation' to diminish the hindrance of breath excursions on focusing the stones. In this way the stones remained as long as possible in the focal area of the shock waves. Because administration of the shock waves by the Lithostar caused little pain only one of these patients needed general anaesthesia, 43 patients received analgesia and sedation (usually intravenous fentanyl and midazolam) and five patients needed no analgesia at all. None of the patients in this group received 'high-frequency jet ventilation' With the Lithostar, 44 patients were treated in the prone position, two in the supine position and three in the left lateral position

In all patients the stones were visualized by fluoroscopy after injection of contrast material (Telebrix 38®, Laboratoire Guerbet, Aulnay, France) into the common bile duct via the nasobiliary drain, post-surgical T tube or percutaneous transhepatic catheter. All treatments were performed under intravenous antibiotic prophylaxis (amoxycillin 1 g intravenously 1 h before ESWL and 8, 16 and 24 h thereafter, and gentamicin 1·5 mg/kg body weight intravenously 1 h before ESWL and 8 and 16 h thereafter).

The day after ESWL treatment the fragmentation results were evaluated by cholangiography If the remaining fragments were considered too large to be evacuated by either biliary drainage, endoscopic measures or percutaneous transhepatic procedures, another ESWL session was undertaken. Chest radiography and ultrasound examination of the upper abdomen were carried out White blood cell count and serum levels of bilirubin, liver enzymes and amylase were determined. Biliary lavage with sterile water (4 litres per 24 h) was started when fragmentation of the largest stone was observed at cholangiography. When total clearance of the common bile duct could not be achieved with biliary lavage, endoscopy or a percutaneous transhepatic procedure to extract the fragment was undertaken

Statistical evaluation of the data was performed by the Mann–Whitney *U* test

Results

Success rate

Dornier HM-3 group. Ten of the 13 patients had one session, two patients had two sessions and one patient had three sessions. The patients treated with the Lithostar had more treatment sessions ($P<0·05$) and needed more shock waves ($P<0·001$) (*Table 2*).

Stone disintegration and clearance of the CBD was achieved in all patients (*Figure 1*). In three patients the CBD was cleared of stone fragments with biliary lavage. Ten patients needed adjuvant intervention to clear the common bile duct. In nine cases this was achieved by endoscopic extraction of stone fragments. In one patient it was necessary to clear the common bile duct by a percutaneous transhepatic approach because endoscopic extraction was impossible due to a previous Billroth II gastric resection.

In one patient one small stone remained in the right hepatic duct but caused no bile obstruction or pain. None of the patients needed emergency surgery. Median hospitalization time after the final ESWL treatment was 14 days (range 4–26 days).

Siemens Lithostar group. Nineteen patients had one session, 16 patients had two sessions, 12 had three sessions and two had four sessions. In this group of 49 patients fragmentation of stones was achieved in 42 patients (86 per cent). Stone clearance of the common bile duct was obtained in 36 patients (73 per cent). Biliary lavage resulted in complete clearance of the common bile duct in eight patients. Endoscopic removal of fragments was successful in 25 patients while three patients needed percutaneous transhepatic clearance of the bile ducts.

Total clearance of the common bile duct could not be obtained in six patients although fragmentation was observed at post-ESWL cholangiography. Endoscopic placement of an endoprosthesis, which was impossible before ESWL, was successfully achieved in three of these patients. The other three patients had a choledochotomy, two in an elective setting and in one patient emergency surgery was necessary. In this last patient attempted endoscopic extraction of fragments in an impacted Dormia basket was complicated by perforation of the common bile duct. Surgical exploration of the common bile duct after cholecystectomy showed fragmented stones in a perforated duct.

In seven patients in whom no fragmenation was achieved, an elective choledochotomy was carried out Median hospitalization time after the final ESWL treatment was 16 days (range 1–76 days).

Complications and side effects

Eleven of the 13 patients treated with the HM-3 had transient macroscopic haematuria (among which one patient had a subcapsular haematoma of the right kidney), while none of the patients who underwent ESWL treatment with the Lithostar

Table 2 *Treatment characteristics of ESWL of common bile duct stones*

	HM-3 ($n=13$)	Lithostar ($n=49$)
Average number of sessions	1·3(0·2)	1·9(0·1)*
No of shock waves per session	1983(170)	4441(116)†
No. of shock waves per patient	2534(513)	8611(693)†
Position (no of patients):		
Supine	13	2
Prone	0	44
Left lateral	0	3
Anaesthesia (no of patients):		
General	13	1
Intravenous analgesia and sedation	0	43
None	0	5

Values are given as mean(s.e.m.), * $P<0·05$, † $P<0·001$

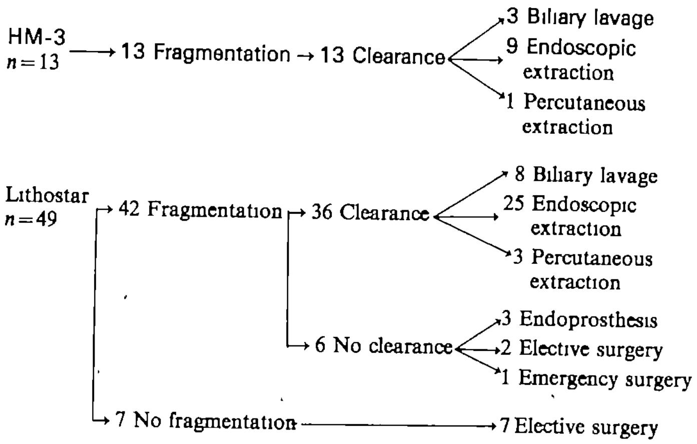

Figure 1 *Results of extracorporeal shock wave lithotripsy of retained common bile duct stones using two different lithotriptors. HM-3 refers to Dornier HM-3, Lithostar refers to Siemens Lithostar®*

Table 3 *Laboratory findings before and after ESWL of CBD stones*

	HM-3 ($n=13$)		Lithostar ($n=49$)	
	Pre-ESWL	Post-ESWL†	Pre-ESWL	Post-ESWL†
White cell count (4·0–10·0 × 10^9/l)‡	9·5 (4·9–14·2)	6·8* (4·1–9·7)	8·0 (3·9–31·4)	7·4 (4·2–11·4)
Bilirubin (2–12 μmol/l)‡	36 (5–179)	13* (4–48)	19 (6–203)	12† (5–65)
Alkaline phosphatase (25–75 units/l)	194 (72–327)	113 (62–310)	178 (53–839)	126† (32–537)
γ-GT (5–35 units/l)‡	110 (20–318)	94 (30–193)	130 (14–746)	67† (16–451)
Aspartate aminotransferase (5–30 units/l)‡	53 (14–425)	24 (13–58)	27 (12–522)	26 (11–192)
Alanine aminotransferase (5–30 units/l)‡	64 (19–775)	26 (10–197)	34 (9–449)	25* (6–196)
Alpha-amylase (30–130 units/l)‡	97 (28–404)	70 (30–130)	86 (31–311)	105 (39–190)

Values are presented as median with ranges in parentheses; † values after the final ESWL treatment; ‡ laboratory reference values, * $P<0·05$, † $P<0·01$ *versus* values before ESWL for either lithotriptor

had haematuria. In the Lithostar group one patient had a transient subcapsular haematoma of the right kidney as demonstrated with ultrasound imaging. Chest radiography 1 day after treatment showed no abnormalities in both groups. Liver haematoma and pancreatitis were never observed. Sepsis with positive blood cultures (*Pseudomonas aeruginosa* and *Escherischia coli*) occurred in two patients (one in each group) and resolved rapidly with antibiotic treatment (piperacillin and gentamicin) and intravenous plasma administration. There was no hospital mortality in either group.

Serum levels before the first and after the final ESWL treatment are presented in *Table 3*. Serum bilirubin and transferase values decreased to nearly normal values. Mean γ-GT and alkaline phosphatase values decreased also after ESWL, but remained higher than the upper limit of the reference values.

Follow-up

Median follow-up time in the HM-3 group was 43 months (range 1–55 months). In this period two patients died of non-biliary causes and two other patients were lost to follow-up 1 and 4 months after the final ESWL treatment without biliary symptoms or signs. The remaining nine patients have had no biliary problems since their final ESWL treatment. Patients treated with the Lithostar had a median follow-up time of 18 months (range 2–37 months). In this group four patients died of non-biliary causes. None of these patients (including the patients who underwent surgery) had biliary symptoms or signs after their last treatment.

Discussion

Since the introduction of endoscopic sphincterotomy, treatment of common bile duct stones has changed dramatically. At present, surgical choledochotomy is no longer always the therapy of choice due to its invasive character and associated morbidity and mortality rates. Extracorporeal shock wave lithotripsy (ESWL) offers a non-surgical alternative when endoscopic stone extraction fails.

A total of 62 consecutive patients with retained common bile duct stones were treated with ESWL on two different lithotriptors, the Dornier HM-3 lithotriptor using the electrohydraulic principle and the Siemens Lithostar using an electromagnetic principle. Stone clearance after the final ESWL treatment was achieved in 79 per cent of the patients who otherwise would have been subjected to surgical exploration. After fragmentation, stone clearance was achieved by biliary lavage in 11 patients, by endoscopy in 34 patients and by percutaneous transhepatic approach in four patients[36].

There are important differences between the two lithotriptors with regard to patient management. Firstly, patients in the HM-3 group were treated under general anaesthesia as shock waves at maximum energy level caused too much pain to be controlled by intravenous analgesia and sedation. General anaesthesia has the advantage that from the beginning of treatment shock waves can be delivered at maximum energy level We must emphasize that the Dornier HM-3 is a first-generation lithotriptor (with waterbath). As others have demonstrated, ESWL treatment with the modified Dornier lithotriptor without waterbath is also possible without general anaesthesia[32] In patients treated with the Lithostar, pain caused by the shock waves could be managed satisfactorily by intravenous analgesia and sedation Use of this type of analgesia implies that the generator voltage can only be gradually increased. Secondly, patients treated with the HM-3 had 'high-frequency jet ventilation' to diminish the breath excursions. With this type of artificial respiration the stones remained in the focal energy area of the shock waves as long as possible. Patients with intravenous analgesia and sedation (Lithostar) are not suitable for 'high frequency jet ventilation'. Thirdly, patients with the HM-3 were treated in the supine position whereas most patients (44/49) with the Lithostar were treated in the prone position. Interposition of bowel gas presumably absorbs shock wave energy[37]. This is more likely to occur in the prone than in the supine position.

Although the ultimate results, defined as fragmentation rate and common bile duct clearance, are comparable for these two lithotriptors, there is a trade-off between the type of anaesthesia and the intensity of treatment. This results from the inherent differences in focal geometry of these two lithotriptors[38,39]. The HM-3 at the 21 kV discharge potential produces pressures up to 38·6 MPa in a focal area of 20 × 120 mm, whereas the Lithostar at the 19·0 kV level generates pressures up to 32·5 MPa in a focal area of 9 × 95 mm. Patients treated with the Lithostar needed more sessions and more shock waves per session but did not need general anaesthesia, which is an advantage in this relatively elderly high-risk population.

Regarding side effects, transient macroscopic haematuria was frequently observed in the patients treated with the HM-3 lithotriptor. Two patients, one in each group, developed a subcapsular haematoma of the right kidney. Ultrasound imaging at follow-up showed complete disappearance of the haematomas within 4 and 6 days. Although these complications had no clinical sequelae, the long-term effects of such complications are unknown. Recently Williams *et al*[40] reported the long-term side effects of renal lithotripsy, 8 per cent of the patients treated with ESWL for renal stones developed sustained hypertension after ESWL Concern about these complications is necessary, because during ESWL treatment of common bile duct stones, shock waves may traverse the right kidney

One patient in each group developed sepsis in spite of treatment under 24 h antibiotic prophylaxis. However, these two patients also suffered from septic episodes before ESWL treatment. There was therefore no evident relation between the occurrence of sepsis and ESWL, ERCP or percutaneous transhepatic procedures.

We conclude that ESWL of common bile duct stones, after failed endoscopic extraction, offers several advantages over other non-operative therapies. It is a rapid, non-invasive, effective treatment with low complication rates and minimal discomfort for the patient. In our opinion extracorporeal shock wave lithotripsy of retained common bile duct stones should be considered before surgery in the elderly or high-risk patient.

Acknowledgements

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Case report

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Successful reuse of a liver graft

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After organ transplantation patients may suffer brain death (frequently due to massive haemorrhage) thereby becoming a potential donor of those organs which continue to function. The use of kidneys donated under such circumstances following liver or heart transplantation has been described[1] There is no previously reported experience of the reutilization of a liver graft following the brain death of the first recipient.

Case report

Donor

The donor was a 40-year-old female, blood type Rhesus O+, who died as a result of a stab wound. She was actively bleeding and was hypotensive Haemodynamic stabilization was accomplished, yielding a blood pressure of 125/80 mmHg. An electroencephalogram (EEG) revealed absence of brain activity. A dose of 10 $\mu g\,kg^{-1}\,min^{-1}$ dopamine was necessary to maintain the blood pressure. Multiple organ retrieval was carried out and the grafts perfused with Wisconsin solution

Recipient 1

The first recipient was a 57-year-old normotensive female, blood type O+, suffering from primary biliary cirrhosis which had progressed to stage IV. Hepatic transplantation was carried out without complication, except for mild hypotension throughout the procedure which was easily corrected.

The cold ischaemic time of the graft was 1 h 52 minutes and the warm ischaemic time was 1 h The biopsy at time zero showed no ischaemic changes[2]. In the final stages of the operation there was a transient episode of bilateral midriasis which appeared related to the intravenous administration of 2 mg atropine

Immunosuppressive therapy with corticosteroids and azathioprine was commenced. Cyclosporin was administered after 24 h. Postoperative biochemical parameters are shown in *Figure 1* Six hours after admission to the intensive care unit the patient lost consciousness and exhibited bilateral non-reactive midriasis with a blood pressure of 200/100 mmHg A head CT scan revealed intraventricular and basal ganglia haemorrhage No brain activity was found on EEG, and donation of organs was requested.

At laparotomy the liver was noted to be in satisfactory condition with good colour and consistency. Arterial and venous perfusion were normal with intact vascular anastomoses and reuse of the graft was deemed possible The graft was perfused with Wisconsin solution through the aorta and superior mesenteric vein and the liver and both kidneys were removed.

Recipient 2

The second recipient was a 29-year-old female, blood type (ABO) compatible with the graft. She had undergone liver transplantation 15 months previously for biliary cirrhosis, sclerosing cholangitis and a cholangiocarcinoma of the biliary confluence with involvement of one hilar lymph node and one right suprapancreatic lymph node Five months later acute graft rejection occurred which was treated with monoclonal antibodies (OKT 3), but chronic rejection occurred with no evidence of abdominal tumour recurrence.

The vascular anastomoses were formed in the following order·

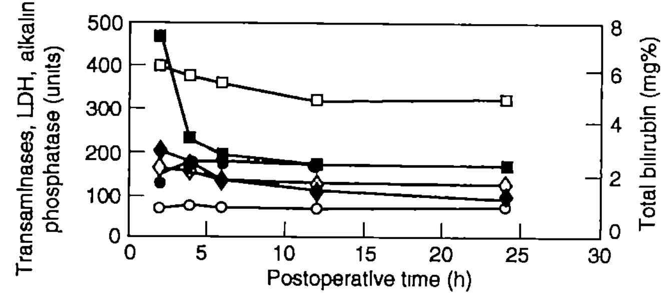

Figure 1 *Postoperative course of biochemical parameters in the first recipient during the first 24 h post-transplantation The satisfactory response of the graft is demonstrated* ■, *Total bilirubin,* ◆, *serum glutamic oxaloacetic transaminase,* ◇, *serum glutamic pyruvic transaminase,* ○, *GGT,* ●, *alkaline phosphatase,* □, *lactate dehydrogenase (LDH)*

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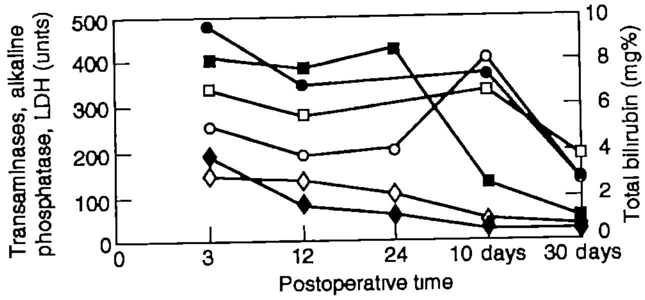

Figure 2 *Postoperative course of biochemical parameters in the second recipient from 3 h to 30 days postoperatively (discharge).* ■, *Total bilirubin,* ◆, *serum glutamic oxaloacetic transaminase;* ◇, *serum glutamic pyruvic transaminase;* ○, *GGT,* ●, *alkaline phosphatase,* □, *lactate dehydrogenase (LDH)*

suprahepatic cava–cava, infrahepatic cava–cava and portal–portal. Splanchnic reperfusion was achieved in 50 min Arterial reconstruction was performed by end-to-end anastomosis of the donor and recipient coeliac trunks. Bile production was noted a few minutes after arterial reperfusion. Cold ischaemic time was 1 h 40 min. Examination of the resected graft revealed evidence of chronic rejection but no sign of recurrent cholangiocarcinoma. Operative biopsy of the new graft revealed grade II cold ischaemic changes[2]

The postoperative course of biochemical parameters is shown in *Figure 2*. Six months post-transplantation the patient continues to be in good health without complications.

Discussion

A reused liver graft is at risk of functional damage secondary to perfusion and storage and parenchymal damage which may occur with extraction and implantation[3,4]. The original transplantation provides an opportunity to study the donor and the response of the organ to implantation (enzyme and coagulative disorders, biliary excretion, etc.). In the first recipient there was a very favourable functional response with bile excretion beginning a few minutes after establishing hepatic blood flow. The levels of serum glutamic pyruvic transaminase (SGPT) and serum glutamic oxaloacetic transaminase (SGOT) reached maxima of only 171 and 209 units, respectively (more or less the same results seen in the postoperative period of the second recipient). This minimal disturbance of hepatic transaminases is a good marker of graft viability[5]. Biochemical response and arterial blood gases and subjective factors (colour, consistency and morphology of the graft) have been used[6–9].

The waiting lists for hepatic transplantation continue to grow, and it is not unusual for the mortality rate to be higher among those awaiting transplantation than for those in the immediate postoperative period[10–12]. Indications for hepatic transplantation in those with malignant disease have decreased due to the unfavourable long-term results[13,14] and the large number of patients with terminal hepatic cirrhosis awaiting transplantation[15–17].

The primary incentive to reuse an organ must be the shortage of donors but in selected cases reutilization may allow prediction of outcome based on the original function of the graft and its response to perfusion and cooling[18,19].

The surgical technique is simplified, involving only division of the vascular trunks and yielding a liver graft which has been previously prepared for implantation.

To reduce the cold ischaemic time to a minimum the liver need not be removed from the first recipient until the second patient is ready to undergo implantation.

A viable graft in a transplant recipient who subsequently dies of other causes may maintain its viability and serve a second recipient, thereby avoiding the loss of useful organs.

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Results of surgery for duodenal ulcer: assessment by patients

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A questionnaire was administered to 224 patients who had undergone 246 operations for duodenal ulcer to see how well this correlated with Visick grading and to provide insight into the patients' feelings about the results of their surgery. The patients were divided into three groups by Visick grade: good (grade I, $n=70$), satisfactory (grades II and IIIs, $n=104$) and poor (grades IIIu and IV, $n=72$). The distribution of questionnaire responses in each group was statistically different ($P<0\cdot01$). Dividing the questionnaire responses into three corresponding groups, 72 per cent of patients assigned themselves to the same group as their Visick grade. Three observations were made regarding the Visick system: recurrent ulceration is over-scored and should be included only if symptomatic; grading should acknowledge a wider range of symptoms related to ulcer disease and its treatment; only three grades are necessary.

The ideal operation for duodenal ulcer disease remains controversial and evaluation usually compares recurrence rates and clinical symptomatic status expressed as a Visick grade[1]. In the last four decades the treatment and natural history of ulcer disease has changed but the grading system has not been re-evaluated. The continued use of the Visick method has tied surgeons to a labour-intensive long-term face-to-face follow-up of patients. Small *et al.* therefore developed a self-administered patient questionnaire to look at specific postoperative problems and general wellbeing after surgery for peptic ulcer[2]. They obtained a good correlation with Visick grading. It has not been further evaluated. The method may provide an impartial outcome assessment, obviate costly and time-consuming clinic attendance and provide insight into the way patients view the outcome of their surgery.

Small's questionnaire was therefore administered to a larger heterogeneous group of patients with two aims in mind. to see if there was a correlation with Visick grading, and to determine whether factors separate patient and surgeon-based assessments of the results of surgery for peptic ulcer disease.

Patients and methods

The questionnaire was given to 224 patients who had had primary or revisional surgery for duodenal ulcer disease at least 1 year previously They comprised all such patients attending a gastric follow-up clinic over an 18-month period They were graded by one of us (J.R.A.) according to the Visick system[3] It was not possible to arrange for a 'neutral' physician to participate in the study, but the original surgery had been performed by other clinicians in 76 per cent of cases. The questionnaire was completed at the clinic at the same time as the Visick grade was assigned. Of the 224 patients, 162 (72 per cent) were men. The mean age was 51 years (range 21–88 years). Follow-up ranged from 1 to 33 years with 53 per cent of patients being assessed 5 or more years after surgery. Twenty-two patients were assessed twice, before and after revisional surgery. Primary surgical procedures were performed electively and as an emergency (39 cases, 17 per cent). The operations were performed by a large number of surgeons throughout Glasgow and involved a range of different procedures summarized in *Table 1*. The raw data therefore comprised 246 questionnaire scores with a contemporaneous Visick grading. Statistical analysis was carried out using the Mann–Whitney *U* test

Results

The distribution of Visick Grades is shown in *Table 2*. Thirteen patients were graded Visick IIIs and five Visick IIIu (7·3 per cent of all cases). The recent literature studying 4776 patients assigned 377 (7·9 per cent) to Visick grade IIIs or IIIu (*Table 3*). The patients were therefore divided into three groups, Visick grade I was left intact (70 patients, good result), and grades II and IIIs were grouped together (104 patients, satisfactory result), as were grades IIIu and IV (72 patients, poor result).

Figure 1 shows the distribution of questionnaire scores in each of the three Visick groups. The clinical relevance of this correlation was assessed by dividing the questionnaire scores into three to correspond to the three Visick groups The cut-off scores providing the best group distinction were 35 and 53. That is, patients whose questionnaire responses gave a score of 35 or lower were regarded as having, by their own assessment, a poor result; those with a score of 53 or above were regarded as having a good result; and those scoring themselves 36–52 were regarded as having a satisfactory result. These groups were compared with the Visick groups in *Figure 2* Seventy-two per cent of patient and surgeon assessments were the same.

Discussion

Reasonable agreement was demonstrated between Visick grades and questionnaire scores, but not of a degree to predict one from the other reliably. The 28 per cent of patients with a Visick assessment differing from the patient's assessment have been examined in further detail.

Table 1 *Operations performed in 224 patients*

Operation	No of patients
Truncal vagotomy and drainage	143
Proximal gastric vagotomy	58
Gastrectomy	12
Other	11

Table 2 *Distribution of Visick grades*

Grade	No. (%) of patients
I	70 (28)
II	91 (37)
IIIs	13 (6)
IIIu	5 (2)
IV	67 (27)

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Table 3 *Proportion of patients assigned to Visick grade III in 20 series*

Report	Ref.	No. of patients	Patients in grade III (%)
Busman and Munting	4	251	8·0
Hoffmann *et al.*	5	103	0·9
Clark *et al.*	6	416	3·6
de Vries *et al.*	7	145	9·7
Choi *et al*	8	153	1·3
Enskog *et al*	9	305	6·9
Liavag and Roland	10	224	2·7
Kennedy	11	242	7·0
Muller *et al.*	12	415	4·3
Thomson and Galloway	13	101	11·9
deMiguel	14	141	2·8
Andersen *et al*	15	395	6·6
Golligher *et al*	16	623	14·6
Dorricott *et al.*	17	160	15·6
Adami *et al*	18	229	10·5
Adami *et al*	19	168	13·7
Kronborg and Madsen	20	100	13·0
Christiansen *et al.*	21	241	8·3
Nilsell	22	118	5·9
Current		246	7·3
Total		4776	7·9

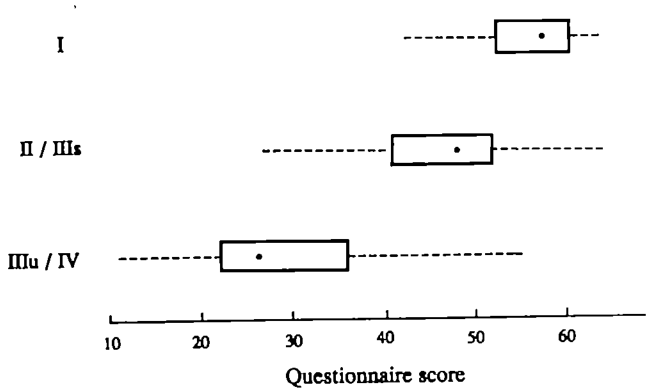
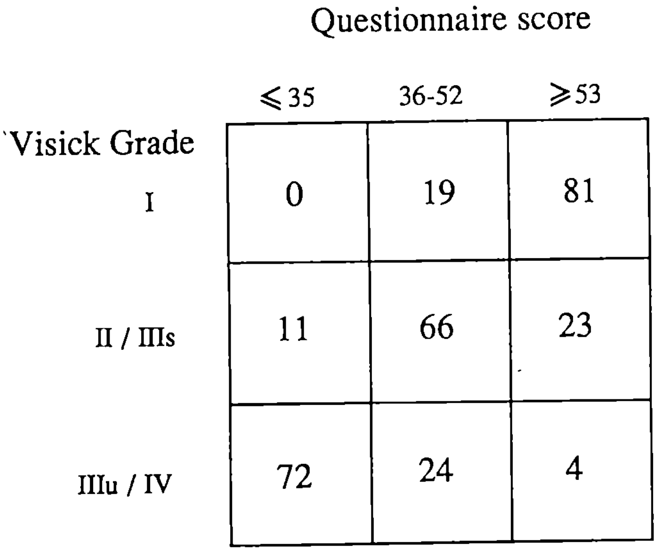


Figure 1 *Distribution of questionnaire scores by Visick grade. Lines indicate range of scores in each group, boxes indicate central quartiles and • indicates median score Comparing groups I* versus *II/IIIs and II/IIIs* versus *IIIu/IV*, P<0·01 (*Mann–Whitney* U *test*)



Visick Grade	Questionnaire score ⩽35	36-52	⩾53
I	0	19	81
II / IIIs	11	66	23
IIIu / IV	72	24	4

Figure 2 *Correlation of questionnaire scores with Visick grade (all figures as percentages)*

Visick grades IIIu and IV with questionnaire scores equal to or greater than 36

Of 67 patients in this group graded Visick IIIu or IV, 18 gave themselves a score above 36 and so were not classed as a poor result by the questionnaire poor group Fourteen had recurrent ulceration; 11 were asymptomatic and three were mildly symptomatic on treatment with H_2-receptor antagonists. In the original Visick grading system[3], recurrent ulceration was automatically and permanently a grade IV result. Some patients with recurrent ulceration feel satisfied with surgery if it ameliorates disease to a degree, enabling it to be controlled by medical therapy. The automatic classification of ulcer recurrence into grade IV should therefore be questioned. Others have made similar suggestions when analysing the outcome of various surgical treatments[23,24]. Busman and Munting[23] postulated that recurrent disease after proximal gastric vagotomy would be mild, but these results suggest a more general explanation. Of the 14 patients with recurrence who scored themselves satisfactory or good, 12 had had a truncal vagotomy and only two a proximal gastric vagotomy. The need for medical therapy needs to be included within any grading system, a patient with a recurrent ulcer but asymptomatic on H_2-receptor antagonists cannot be thought of as having as good a result as an equally well patient who is free of recurrence.

The grading must be regarded as an assessment at a particular time and must be repeated if long-term evaluation is to be assessed. Busman and Munting[4] referred to dynamic grading, but used the Visick system and repeated interviews. The questionnaire allows this concept without interviews.

Visick grades II and IIIs with questionnaire score equal to or less than 35

Of 104 patients in the satisfactory group, 11 scored less than 35 on the questionnaire. Five did so largely because they suffered epigastric pain, but did not have evidence of ulcer recurrence at endoscopy. In the absence of such evidence this pain may be regarded as non-peptic in origin and potentially disregarded in assigning the Visick grade. Another three of this group were unhappy as a result of wound complications; two had an incisional hernia and the other suffered persistent wound pain. Such problems are a direct result of surgery. We therefore suggest that the Visick system be broadened to take account of such problems.

The distribution of grades within the study population, with few patients classified as Visick grade III, seems to be typical (*Table 3*) In practice grade III is rarely used and can therefore be removed from the system.

These results suggest the following changes in a system used to assess the results of surgery for peptic ulcer disease (*Table 4*).

1. Recurrent ulceration receives too much emphasis in the Visick system Patients should be assessed on symptoms alone, taking account of any treatment they are recieving.
2. Grading should take account of all symptoms related to ulcer disease and its treatment, not just gastrointestinal symptoms specific to it.
3. Only three grades are being distinguished in practice. The current grades IIIs and IIIu are little used and can be dispensed with.

It would seem acceptable to use the questionnaire-derived data

Table 4 *Suggested modified grading system*

Grade	Definition
A	No symptoms referable to ulcer disease or its treatment, no need for medication
B	Presence of symptoms, but easily controlled by treatment or care; symptoms not completely controlled, but not interfering with work or enjoyment of life
C	Symptoms which even on treatment are severe or interfere with work or enjoyment of life

to give a dynamic view of the surgical result This provides a useful means of assessing the results of surgery for peptic ulcer and for comparing the results of different operations. The questionnaire is now being used to supplant clinic visits. In the current financial climate the savings made this way are highly relevant

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Problems in the definition and treatment of early gastric cancer

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Radical operation with extensive dissection of lymph nodes (R_1, 48 patients; R_2, 196 patients; R_3, one patient) was performed in 245 out of 247 patients with early gastric cancer. The 5-year survival rate was only 73·2 per cent in the 34 patients with lymph node metastases (31·8 per cent). Analysis of factors influencing recurrence revealed that not only lymph node metastases but also the depth of cancer invasion could affect prognosis in early gastric cancer. This study suggests that radical operation with complete dissection of the first and second group of lymph nodes (R_2 resection) is a safe and appropriate treatment even for early gastric cancer. We propose that the definition of early gastric cancer be modified to 'carcinoma with invasion confined to the mucosa or submucosa and without evidence of lymph node metastases'.

Recent developments in diagnosis and the introduction of mass screening programmes have allowed increased detection of early gastric cancer, leading to an excellent survival prospect. Although the overall 5-year survival rate for patients with early gastric cancer has improved from 60 per cent to over 90 per cent[1–7], the problem of cancer recurrence remains[8]. This study was undertaken to clarify the surgical treatment of early gastric cancer, with special reference to lymph node metastases. In addition, problems regarding the definition of early gastric cancer[9] are discussed.

Patients and methods

From 1975 to 1987, 247 patients with early gastric cancer (174 men and 73 women) underwent resection in the Department of Surgery I, Kyoto University Hospital. This represents 29 2 per cent of all patients with primary gastric cancers who underwent gastrectomy in the unit over the same period (845 patients). The operative procedures included subtotal gastrectomy (212 cases), total gastrectomy (32 cases) and proximal gastrectomy (3 cases). A 5 cm proximal and distal gastric clearance in the unstretched stomach was obtained regardless of gastrectomy type. Gastric resection based on lymph node dissection was classified into four types (R_0, R_1, R_2 and R_3) according to the extent of the removal of the respective lymph node group[9]. Two cases of R_0, 48 cases of R_1, 196 cases of R_2 and one case of R_3 resection were performed. The R_2 gastric resection was attempted whenever possible This involved *en bloc* dissection of all contiguous lymphatics and the first (right paracardial region, left paracardial region, along lesser curvature, along greater curvature, suprapyloric region and infrapyloric region) and second (along left gastric artery, along common hepatic artery, around coeliac axis, at splenic hilus, along splenic artery) groups of lymph nodes, with removal of the entire greater omentum, superior leaf of the mesocolon, pancreatic capsule and lesser omentum. Curative gastric resection was performed in all but two cases, both of whom were found to have advanced and distant lymph node metastases. Histopathological examination was carried out to determine the depth of cancer invasion, histological type and presence of lymph node metastases. The depth of invasion of the submucusal (sm) cancer was further divided into three subgroups according to the extent of invasion (sm_1, sm_2 and sm_3) (*Figure 1*) The macroscopic classification, anatomical distribution, numbering of the regional lymph nodes, extent of lymph node dissection and stage grouping (*Table 1*) were evaluated based on the general rules for gastric cancer study in Japan[9] The patients were followed at 1–2 month intervals for 1 year after operation and thereafter at 3–6 month intervals. Follow-up information was obtained by routine clinical appointments or telephone contact with the patient, family or local physician. Examination for upper gastrointestinal cancer, using endoscopy and ultrasonography, was performed yearly for early detection of cancer recurrence. If symptoms or physical signs suggestive of recurrence developed or if serum tumour markers were elevated, patients were investigated by CT or chest radiography as well as the above mentioned examinations. Cumulative survival rates were calculated using Kaplan-Meier analyses with exclusion of patients who died of diseases unrelated to gastric cancer. The Cox proportional hazards model was used to test the association of the numerous variables with survival. A P value of less than 0·05 was considered statistically significant

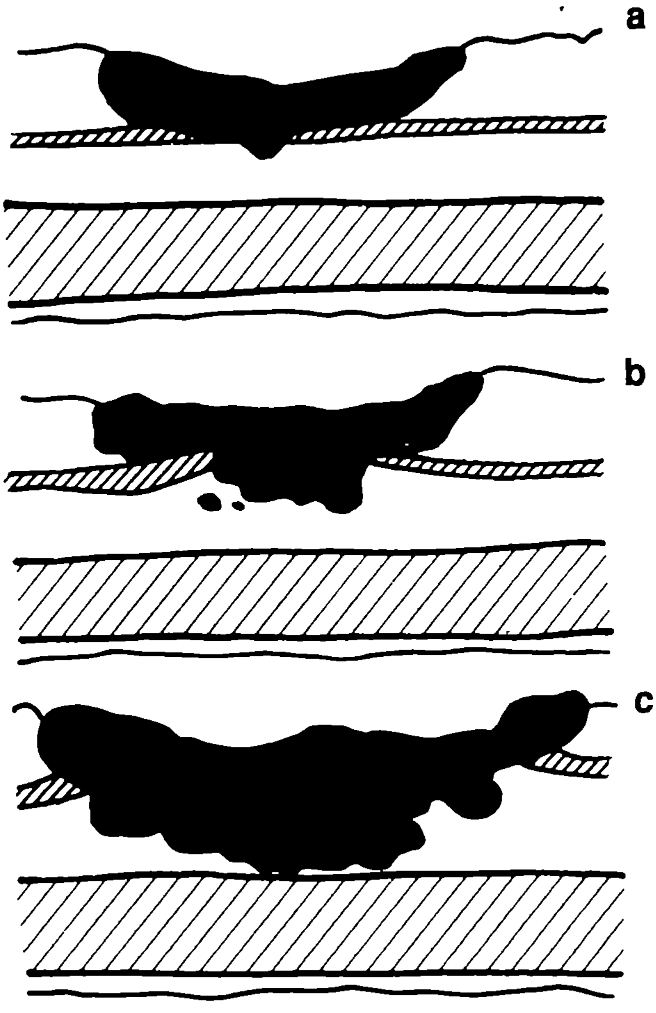

Figure 1 *Subdivision of the submucosal (sm) cancer according to the extent of depth of cancer invasion.* **a** *sm_1, slight invasion limited in the upper submucosa;* **b** *sm_2, moderate invasion into the middle of the submucosa;* **c** *sm_3, deep submucosal invasion close to the muscular layer*

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Table 1 *General rules for stage grouping in Japan*

Stage	Lymph node metastasis	Serosal invasion	Peritoneal dissemination	Liver metastasis
I	n(−)	−	−	−
II	$n_1(+)$	+	−	−
III	$n_2(+)$	+	−	−
IV	$n_3(+)$, $n_4(+)$	Invasion to contiguous structure	+	+

Results

No operative death, defined as the death within 30 days of the surgical procedure or before discharge from hospital, was recorded. The postoperative course was uneventful except for wound infection (two patients), respiratory complications (two patients) and bleeding (one patient)

Of the 247 patients, 125 had lesions confined to the mucosa and 122 had lesions invading to the submucosa. The overall 5-year survival rate was 94·4 per cent. The 5-year survival rate in patients with mucosal cancer was significantly higher than in patients with submucosal cancer (100 per cent and 90 per cent respectively; *Figure 2*). Metastatic lymph nodes were identified histopathologically in 34 cases (13·8 per cent). The 5-year survival rate in these patients (73 2 per cent) was significantly lower than for those without lymph node metastases (99·4 per cent) (*Figure 3*). Lymph node metastases were much more common in submucosal cancer (23·8 per cent; 29 cases) than in mucosal cancer (4·0 per cent; 5 cases) (*Table 2*).

Based on lymph node examination there were 22 Stage II patients ($n_1(+)$), 10 stage III patients ($n_2(+)$) and 2 stage IV patients ($n_3(+)$) (*Table 1, Table 2*) in the entire series of 247 patients. The 5-year survival rate in submucosal cancer patients with metastatic lymph nodes was 69 per cent whereas if lymph nodes were not involved, it was 98·5 per cent (*Figure 4*).

Macroscopic observation of the gastric lesions revealed 15·5 per cent to be of the elevated type, 1·4 per cent of flat type, 60 7 per cent of depressed type and 22·4 per cent of mixed type. Histopathological examination indicated the presence of papillary adenocarcinoma (6·3 per cent), tubular adenocarcinoma (57·5 per cent), poorly differentiated adenocarcinoma (23·1 per cent), signet-ring cell carcinoma (12·2 per cent) or mucinous adenocarcinoma (0·9 per cent).

Factors influencing the recurrence after gastric resection in patients with early gastric cancer are analysed in *Table 3*. Recurrence occurred in three patients with sm_2 lesions, five with sm_3 tumours, and one with an sm_1 lesion. Lymph node metastases were found in three patients with $n_1(+)$ lesions, four with $n_2(+)$ lesions and one with $n_3(+)$ lesions.

Discussion

It is widely accepted that gastric cancer is diagnosed early with increasing frequency and has excellent survival prospects after treatment, not only in Japan[1,2] but also in other countries[3–7]. The present study also demonstrates an excellent 5-year survival rate (94·4 per cent). Early gastric cancer is at present defined as 'carcinoma with limited invasion to the mucosa or submucosa' regardless of lymph node metastases. This study, however, reveals that the 5-year survival rate for early gastric cancer showed unexpectedly low values (73·2 per cent), when lymph node metastases are present, in comparison with the survival rate of patients without lymph node metastases (99·4 per cent) (*Figure 3*). Furthermore, analysis of factors influencing the recurrence after gastrectomy clearly indicates that the depth of cancer invasion also strongly affects the prognosis, since a very high frequency of recurrence was found in sm_2 and sm_3 cancer (*Figure 1, Table 3*).

These data raise the question as to whether the definition of early gastric cancer is still pertinent. Although sm_2 and sm_3 cancer could be excluded from early gastric cancer, the new definition of early gastric cancer as carcinoma with invasion confined to the mucosa or submucosa 1 (sm_1) is somewhat complicated. One of the most important messages of our paper is that 13·8 per cent of patients with early gastric cancer had histologically confirmed lymph node involvement with unexpectedly low survival rates relative to patients with no lymph node metastases. Thus 13 8 per cent of patients with early gastric cancer can be classified in stages II–IV (*Table 1*)[9].

It does not appear logical that this proportion of patients with early gastric cancer belong to stage II or more advanced

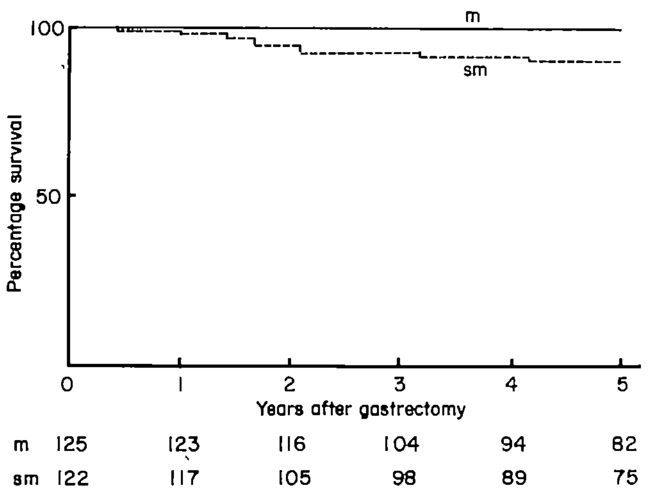

Figure 2 *Cumulative survival rate of mucosal (m) and submucosal (sm) gastric cancer (total number of patients, 247) ——, m (125), -----, sm (122);* P<*0·001. The number of patients eligible for analysis at each of the time points is shown below the x-axis*

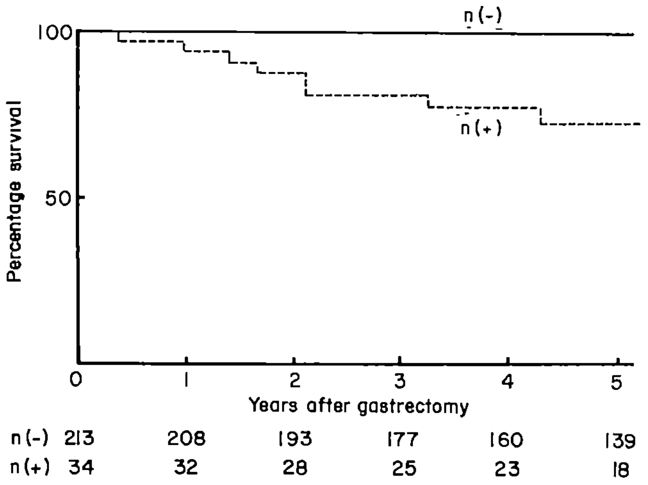

Figure 3 *Cumulative survival rate of early gastric cancer with (n(+)) and without (n(−)) lymph node metastases (total number of patients 247) —— n(−) (213), ----- n(+) (34);* P<*0 01 The number of patients eligible for analysis at each of the time points is shown below the x-axis*

Table 2 *Relationship between depth of invasion and lymph node metastases*[9] *in 247 patients with early gastric cancer*

Depth of invasion	Number of patients				
	n(−)	n(+)	$n_1(+)$	$n_2(+)$	$n_3(+)$
Mucosal	120 (96·0)*	5 (4·0)	4	1	0
Submucosal	93 (76·2)	29 (23 8)	18	9	2

* Numbers in parentheses are percentages

Table 3 *Nine deaths caused by cancer recurrence*

Patient	Recurrence pattern	Depth of invasion	Lymph node metastasis	Location	Macroscopic type	Tumour size (cm)	Histologic type	Postoperative survival duration (months)
1	Skin and lung metastasis	sm_3	$n_2(+)$	A	IIc	2·3 × 2·3	Por	51
2	Peritoneal dissemination	sm_3	$n_2(+)$	C	IIc	2·0 × 2·5	Tub	38
3	Lung metastasis	sm_2	$n_1(+)$	M	IIc + III	3·0 × 3·5	Por	37
4	Peritoneal dissemination	sm_1	$n_1(+)$	M	IIc	3·5 × 4·0	Por	24
5	Liver metastasis	sm_2	$n_2(+)$	A	IIa + IIb	4·3 × 5·5	Tub	20
6	Liver metastasis	sm_2	$n_1(+)$	C	IIa	2·0 × 2·5	Por	18
7	Peritoneal dissemination	sm_3	$n(-)$	MA	IIc	4·5 × 5·5	Por	18
8	Lymph node metastasis	sm_3	$n_2(+)$	A	IIc + III	3·0 × 3·5	Tub	12
9	Lymph node metastasis	sm_3	$n_3(+)$	M	IIa	5·2 × 7·0	Tub	6

A, antrum; M, mid-portion of the stomach; C, cardia; Por, poorly differentiated; Tub, tubular adenocarcinoma

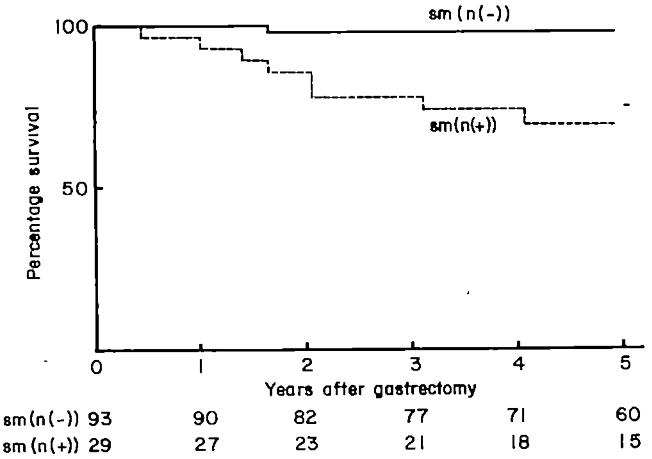

Figure 4 *Cumulative survival rate of submucosal (sm) gastric cancer with (n(+)) and without (n(−)) metastatic lymp node involvement (total number of patients 122) —— sm(n(−)) (93), ---- sm(n(+)) (29), P<0·01. The number of patients eligible for analysis at each of the time points is shown below the x-axis*

stages with their relatively high risk of cancer recurrence: it would be easier to accept if early gastric cancer were defined as carcinoma which is confined to the mucosa or submucosa but not exceeding stage I However, in stage I gastric cancer invasion to the muscular layer proper or subserosal layer is occasionally included. Therefore, it seems more pertinent to define early gastric cancer as 'carcinoma with invasion confined to the mucosa or submucosa and without evidence of lymph node metastases'.

Concerning surgical treatment, radical operation with extensive dissection of lymph nodes was performed in 245 of our 247 patients. It seems very likely that the extensive lymphadenectomy led to the high survival rate for early gastric cancer, since 13·8 per cent of patients had involved lymph nodes including the first, second and third groups (*Table 2*).

Lymphadenectomy contributes to the improvement in survival rate in gastric cancer[10,11]. There has however, been no established surgical procedure for treating early gastric cancer, especially regarding extensive lymphadenectomy. It is widely recognized that lymph node metastases affect survival of early gastric cancer as well as that of advanced gastric cancer[12–14]. We consider it time to evaluate the extent to which lymphadenectomy should be performed during gastric resection for early gastric cancer. Complete dissection of only the first group of lymph nodes (R_1 operation) will suffice for the mucosal cancer, because very few lymph node metastases are present. Given the developments in the endoscopic assessment of the depth of cancer invasion, it is likely that endoscopic treatment[15,16] may be actively used in mucosal cancer instead of surgical treatment in the near future.

For submucosal cancer R_2 operation (complete dissection of the first and second group of lymph nodes) is preferable because of the relatively high frequency of lymph node metastases. In the very rare cases of distant lymph node metastases such as $n_2(+)$, R_3 operation should be performed if possible. If lymph node metastases are too advanced to allow curative resection, adjuvant therapy is recommended as for advanced cancer The current problem, however, lies in the difficulty of accurately diagnosing preoperatively the depth of cancer invasion, and in discriminating mucosal cancer from the submucosal cancer by endoscopy or other methods

Accordingly, at present, we recommend R_2 operation as a safe and optimal procedure for early gastric cancer until the precise preoperative diagnosis of the depth of cancer invasion becomes available. The relatively low 5-year survival rate in early gastric cancer patients with lymph node metastases suggests that adjuvant chemotherapy or immunotherapy should be given to these patients. It is possible that in the future, endoscopic treatment might be applicable even in submucosal cancer if diagnostic techniques allow determination of whether lymph nodes are involved by metastases

In conclusion, this study leads us to propose that the definition of early gastric cancer may need some revision, since the survival of early gastric cancer is almost as low as the same stage of advanced cancer when lymph nodes are involved by metastases. The definition of early gastric cancer might be modified to 'carcinoma with invasion confined to the mucosa or submucosa and without evidence of lymph node metastases' We also suggest that radical operation with extensive dissection of the first and second group of lymph nodes is a safe and appropriate surgical treatment, even for early gastric cancer

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Surgical treatment of carcinoma of the gastric stump

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To evaluate retrospectively the surgical treatment of patients with gastric stump cancer following gastrectomy for benign disease, we reviewed 52 patients operated on at the National Cancer Centre, Tokyo, between 1962 and 1988. Resection was carried out in 47 patients (90 per cent) and with curative intent in 36 (69 per cent). Stage distribution was: stage 1, 15 patients; stage 2, 5; stage 3, 9; stage 4, 23. In 36 cases curatively resected, 32 had completion total gastrectomy and four had subtotal resection. An R_1 resection was performed in 11 patients and an R_2 in 25. We had two hospital deaths and a 5-year survival rate excluding hospital deaths of 39 per cent. The 5-year survival rates of resected cases, curative cases and those having metastatic nodes were 43 per cent, 57 per cent and 29 per cent respectively. Radical resection is a reasonable treatment for gastric stump cancer as it is for primary cancer of the stomach.

Although gastrectomy is now performed less frequently for benign disease since the advent of histamine H_2-receptor antagonists[1,2] significant numbers of patients with carcinoma of the gastric stump continue to present because it usually takes >20 years for the tumour to develop[3–6]. Few papers on this subject have dealt specifically with treatment and the published results of survival have been poor as most patients have advanced disease when diagnosed[7–9]. Only a few authors have published their 5-year survival rates and these are usually <10 per cent[7–9].

At present there is considerable interest in the surgical treatment of gastric cancer in the West[10–12], prompted by the improved survival rates obtained in Japan by the use of radical gastrectomy[13]. In studies reporting the results of treatment of gastric cancer, the results of treatment of cancer of the gastric stump are always excluded. However, with increased surveillance of gastrectomized patients[4–6] more of these tumours may be seen at an earlier stage when surgical treatment is more likely to be successful[14].

In Japan, gastric stump cancers are often detected at an early stage and in the authors' unit, the stage distribution of these tumours is comparable to that of tumour arising *de novo* in the proximal third of the stomach. The purpose of this paper is to evaluate retrospectively the surgical treatment of patients with gastric stump cancer following gastrectomy for benign disease.

Patients and methods

Between 1962 and 1988, 6169 patients underwent surgery for gastric cancer at the National Cancer Centre Hospital, Tokyo. Of these, 113 were patients who had previously undergone gastric surgery. All 61 patients who had previously had malignant disease have been excluded and only the 52 patients who had undergone resection for benign disease will be considered further The data obtained have been compared with those of 656 patients with primary gastric cancer of the proximal third of the stomach who were operated on during the same period The mean age was 56·8 years and 60·1 years for tumours of the stump and proximal third of stomach respectively, and the male to female ratio was 6·43:1 and 3·15.1 The reasons for previous gastrectomy were as follows· gastric ulcer in 36 patients, duodenal ulcer in 11 and other miscellaneous conditions such as gastric polyp in five. One patient had undergone a transverse segmental gastrectomy, but the remaining 51 patients had a distal gastrectomy which was reconstructed as a Billroth I in 15 patients and Billroth II in 36. In 12 of them (23 per cent) gastric stump cancer was detected by either a personal annual check or a screening programme in the absence of symptoms. The rest underwent endoscopy or radiological examination after development of upper gastrointestinal symptoms

The site of the tumour within the gastric stump was classified as cardia, fornix or body, anastomotic site or entire stump (*Figure 1*) Macroscopic type of tumour, depth of invasion, lymph node staging, histological type, stage and extent of regional lymphadenectomy were analysed according to the rules of the Japanese Research Society for Gastric Cancer (JRSGC)[15] and TNM system[16] These systems do not take account of lymph nodes in the mesentery of the jejunum anastomosed to the stomach after Billroth II reconstruction As these nodes are often involved with metastases, but may be resectable, this station has been classified separately as a level 2 station and named 'nj'. The incidence of metastases in each lymph node station has been calculated by dividing the number of patients with involved nodes by the number of those who had undergone dissection of that particular station. Survival was evaluated by life table methods and the χ^2 test was employed to assess statistical significance

Results

Pathology

The tumour location, classified according to its main location was: cardia = 10, fornix or body = 16, anastomotic area = 19 and whole stump = 7. The macroscopic tumour type was: Borrmann1 = 5, Borrmann2 = 14, Borrmann3 = 18, Borrmann4 = 6, and early gastric cancer = 9. The histological type was: papillary = 2, tubular 1 = 15, tubular 2 = 14, signet ring cell = 3, mucinous = 3 and poorly differentiated = 15.

The depth of invasion in the 47 resected cases was: pT1 = 9 (mucosa = 5, submucosa = 4), pT2 = 11 (muscularis propria = 4, subserosa = 7), pT3 = 15 (serosa), pT4 = 12 (neighbouring organs). According to the JRSGC rules the staging was as

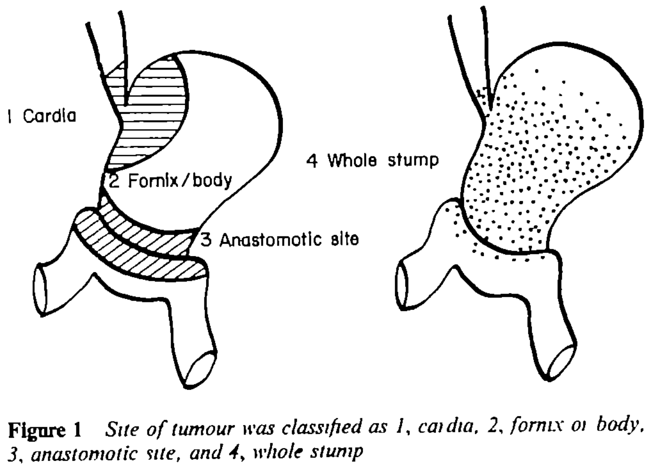

Figure 1 *Site of tumour was classified as 1, cardia, 2, fornix or body, 3, anastomotic site, and 4, whole stump*

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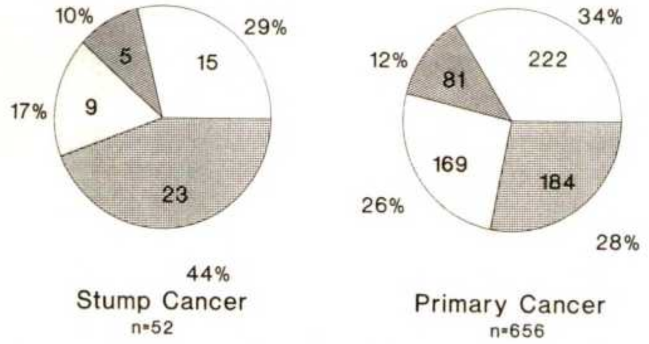

Figure 2 *Stage distribution of stump and primary cancers. Numbers in the circles demonstrate the actual number at each stage and the number outside the circle is the percentage.* □, *Stage 1;* ▨, *Stage 2;* ▩, *Stage 3;* ░, *Stage 4. In stage 4 only was there a statistically significant difference between the two groups* (P<0·05). *If unresectable cases are excluded, there were no statistical differences in any stage*

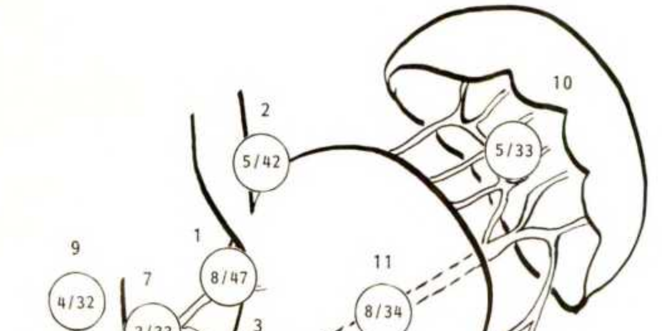

Figure 3 *Numbers x/y in circle denote that among y cases of patients who underwent lymph node dissection of that particular station, x cases had metastases in that node station. Bold numbers indicate the lymph node stations according to the Rules of the Japanese Research Society for Gastric Cancer (see* Table 1). *'nj' means lymph nodes in the jejunal mesentery*

follows: stage 1=15, stage 2=5, stage 3=9, stage 4=23 (*Figure 2*). According to the new TNM rules the staging was: stage Ia=9, stage Ib=7, stage II=8, stage IIIa=2, stage IIIb=5, stage IV=21. pN staging in 36 patients having curative resection was: n0=22, n1=4, n2=10 (including four cases with nj involved).

The incidence of lymph node involvement is shown in *Figure 3* and compared with that found in primary gastric cancers in *Table 1*. In patients undergoing resection oesophageal invasion occurred in 19 cases and jejunal invasion was found after Billroth II in 11 of 36 cases and duodenal invasion after Billroth I in three of 15 cases.

Surgical technique

Resection was possible in 47 patients of whom five had partial resection of the gastric stump while the remainder had completion total gastrectomy. Gastroenterostomy alone was performed in three patients and exploratory laparotomy only in two. Resection was carried out with curative intent in 36 patients. Factors precluding curative resection were peritoneal metastases in eight patients, unresectable invasion of surrounding organs in four, para-aortic lymph node metastases in three and liver metastases in one. In the patients undergoing curative resection, 32 had completion total gastrectomy. In certain cases the following procedures were performed in combination: left thoracotomy because of oesophageal invasion ($n=4$), splenectomy without distal pancreatectomy ($n=13$), splenectomy with distal pancreatectomy ($n=11$), pancreaticoduodenectomy with splenectomy ($n=1$), transverse colectomy ($n=1$) and liver resection for direct invasion ($n=1$). We performed an R_1 dissection of the lymph nodes in seven patients and an R_2 dissection in 25 patients. A curative subtotal resection (R_1) of the gastric stump was performed in four patients who were suspected before operation of having early gastric cancer.

Morbidity and mortality

The following complications occurred in ten of the 52 patients: anastomotic leakage ($n=5$), pancreatic fistula ($n=2$), intra-abdominal abscess ($n=2$), colonic fistula ($n=1$) and anastomotic stricture ($n=1$). There was one death within 30 days of operation in a patient who had exploratory laparotomy (death from myocardial infarction) and another patient died in hospital from anastomotic leakage after total gastrectomy.

Comparison of primary and stump cancers

The resectability rate was 97 per cent and 90 per cent (not significant) and the resections were curative in 80 per cent and 69 per cent ($P<0·05$) in primary cancers and stump cancers respectively. In the primary cases, 34 per cent were stage 1, 12 per cent stage 2, 26 per cent stage 3 and 28 per cent stage 4 (*Figure 2*). In the stump cancers, 29 per cent were stage 1, 10 per cent stage 2, 17 per cent stage 3 and 44 per cent stage 4 ($P<0·05$ in stage 4). If only resected cases are compared, there was no statistically significant difference in stage distribution.

Survival

The 5-year survival rate according to stage is given in *Table 2* and is compared with that of primary gastric cancer. The overall 5-year survival rate excluding two hospital deaths was 39 per cent. The 5-year survival rate of the resected cases was 43 per cent and that of the curatively resected cases 57 per cent. The survival rate varied according to tumour site; thus for tumours arising at the cardia it was 40 per cent, body 59 per cent, anastomosis 36 per cent but it was only 14 per cent for tumours involving the entire gastric remnant. Patients with tumours involving the oesophagus had a 5-year survival rate of 21 per cent and when the jejunum was involved the rate was 18 per cent. Depth of invasion and nodal status were both shown to influence survival markedly but stage for stage no

Table 1 *Incidence of lymph node metastasis*

Lymph node station	Stump cancer	Primary cancer
1 Right cardia	17	27·3
2 Left cardia	12	14·9
3 Lesser curvature	15*	29·0
4 Greater curvature	17*	7·8
7 Left gastric artery	9	18·0
8 Common hepatic artery	9	6·2
9 Coeliac	13	8·8
10 Splenic hilus	15	10·4
11 Splenic artery	24*	10·4
'nj' Jejunal	15	–

All values are percentages. * Statistical difference between stump and primary cancers, $P<0·05$

Table 2 *5-Year survival rates*

Cases	Stump cancer (%)	Primary cancer (%)
Total	39 ($n=50$)	44·7 ($n=634$)
Stage 1	100 ($n=14$)	84·7 ($n=218$)
Stage 2	40 ($n=5$)	46·2 ($n=78$)
Stage 3	39 ($n=9$)	34·9 ($n=165$)
Stage 4	9 ($n=22$)	7·7 ($n=173$)
Resected	43 ($n=46$)	46·0 ($n=616$)
pT1 (m, sm)	100 ($n=8$)	87·0 ($n=169$)
pT2 (pm, ss)	63 ($n=11$)	60·8 ($n=120$)
pT3 (se)	37 ($n=15$)	30·0 ($n=205$)
pT4 (sei)	8 ($n=12$)	10·7 ($n=122$)
Curative	57 ($n=35$)	58·5 ($n=471$)
pN (−)	78 ($n=21$)	78·8 ($n=275$)
pN (+)	29 ($n=14$)	33·0 ($n=196$)
n1 (+)	50 ($n=4$)	42·6 ($n=93$)
n2 (+)	20 ($n=10$)	25·0 ($n=102$)

These 5-year survival rates are calculated *excluding hospital deaths*. No statistically significant difference was seen between stump and primary cancers

difference in survival was demonstrated between primary and stump cancers.

Discussion

A recent review by Dilin *et al.*[8] in 1985 reported a mean 5-year survival rate of 6·9 per cent in 1690 patients with gastric stump cancer. The poor survival was attributed to the fact that these tumours are often advanced and unresectable and therefore efforts have been directed towards earlier detection in gastrectomized patients[4–6]. Because the Japanese are regarded as a high risk population for gastric cancer, there is no specific cohort programme for gastrectomized patients in Japan. Our relatively high rate of early cancer is not only the result of our screening system but is also due to the general awareness of its risk by all Japanese including general physicians[17]. However, in Western countries, better survival figures have been reported more recently. Pointner *et al.*[14] obtained a 5-year survival rate of 74 per cent in 19 patients with early cancer of the gastric remnant. Gianello *et al.*[18] reported 13 patients, some of whom had advanced cancers, with a 5-year survival rate of 47 per cent, but none of the long-term survivors had evidence of nodal or distant metastases.

In the present series, stage 4 cancers were common (44 per cent) and the proportion undergoing curative resection (69 per cent) was significantly lower than that of patients with primary cancer (80 per cent). This may account for the shorter survival in stump cancer, although the difference was not statistically significant. When long-term survival rates in patients with stump cancer were compared with those of patients with primary cancer according to stage, no difference was apparent. It was clear however that, as suspected, prognosis was related to the depth of tumour invasion and the presence of nodal metastases. Nevertheless, the presence of involved nodes does not mean that the situation is hopeless as even with n2 positive nodes a 20 per cent 5-year survival rate was obtained.

Other bad prognostic signs identified were involvement of the whole stump, oesophagus or jejunum. Of 11 patients with jejunal invasion, five had lymph node metastases in the jejunal mesentery. One of these survived 5 years and we would therefore recommend wide resection of the mesentery (from the origin of each jejunal artery) in such cases.

The pattern of lymph node spread appears to be different in stump cancer compared with that seen in primary cancer. Metastases were significantly more common in stations 4 and 11, but less common in station 3. Lymph drainage from the greater curvature would therefore seem to be of greater importance than that from the lesser curvature and this is probably related to previous resection of the lymph channels along the left gastric vessel. To achieve effective lymph node clearance, a total gastrectomy with splenectomy will therefore be required. Dissection of the splenic artery nodes (No. 11) is essential although it may be performed with or without distal pancreatectomy. In rare cases, where an early cancer is confined to the anastomotic area of a large gastric remnant, subtotal resection of the stump may be possible.

Despite our policy of radical resection, our morbidity and mortality was low. In those patients undergoing resection the hospital morbidity was only 2·1 per cent and all but five of these patients had a total gastrectomy. Anastomotic leakage (including non-clinical minor fistula) occurred in five patients (11 per cent) and other complications were rare. It is therefore concluded that radical resection can be undertaken safely in patients with carcinoma of the gastric remnant.

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Lymph node counts in the upper abdomen: anatomical basis for lymphadenectomy in gastric cancer

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The number of regional lymph nodes was determined in sites relevant to lymphadenectomy in gastric cancer in 30 cadavers. Tissue was cleared by dissolving fatty tissue, thus making lymph nodes with a diameter of at least 1 mm visible. All lymph node stations indicated by the Japanese Research Society for Gastric Cancer were studied. In stations 1–11 (corresponding with R_2 resection) an average of 27 nodes (range 17–44 nodes) was found, whereas stations 1–16 (corresponding with R_3 resection) showed an average of 43 nodes (range 25–64 nodes). These values are higher than those usually obtained from lymphadenectomy for gastric cancer. Striking individual differences in the total number of lymph nodes and the number of single stations was observed. The number of lymph nodes in these investigations are the normal anatomical values and serve as quality control of lymph node dissection in gastric carcinoma.

Most surgeons consider lymph node dissection an essential part of gastrectomy for cancer in that possible metastases are removed and a more radical resection results. Aretxabala *et al.*[1] demonstrated that the number of patients with involved nodes and the total number of metastatic nodes increase when nodes are dissected. On the basis of this finding, extensive dissection may be useful in the treatment of gastric cancer[1–3].

Systematic studies of the complicated gastric lymph drainages were not carried out until 20–30 years ago when the Japanese Research Society for Gastric Cancer (JRSGC[4]) reported 16 lymph node sites as possible locations of metastasis and classified them into three groups (N_1–N_3). They form the anatomical basis for systematic lymph node dissection in the surgical treatment of gastric cancer. Soga *et al.*[5] reported their experience of 530 gastrectomies with lymphadenectomy in which they studied 15 739 nodes: a mean of 30 nodes in the 16 sites indicated by JRSGC. Many surgeons continue to achieve a retrieval of at least 30 nodes. Our experience, using the same surgical technique, produced great variation. This prompted the question: what is the normal anatomical value of lymph node number in JRSGC sites?

Materials and methods

Lymph node dissection was performed at the 16 sites indicated by JRSGC in 30 cadavers. None of the deceased had had an abdominal operation, nor had any of these patients suffered from haematological or lymphatic disease. The duration of this autopsy study was 11 months (October 1988 to August 1989). Age, sex and cause of death are given in *Table 1*.

In each lymph node station we removed the fatty tissue with its included lymph nodes. After a Kocher manoeuvre station number 13 (behind the head of the pancreas) was removed, dissecting retropancreatically but not including portocaval nodes. Lymphadenectomy did not include those nodes reached only by a left pancreatic resection in the left perinephric region.

To make all lymph nodes visible the tissues were treated by a clearing technique described by Schmitz-Moormann *et al.*[6]. The tissue was placed in formalin for 1 day, in acetone for 12 h, and then in pure alcohol for 48 h in an incubation apparatus at a temperature of 50°C. The tissue was stored in xylol for at least 2 h. All lipid was extracted and the preparation, having become transparent, was examined on an illuminated plate. Small lymph nodes measuring at least 1 mm in diameter could be seen. All nodes were examined and proved histologically and the diameter of each was recorded.

The quality of lymph node dissection was controlled retrospectively by studies in 36 patients who had been operated on between March 1987 and March 1989 for gastric cancer and included 20 men and 16 women of average age 63·6 years (range 25–84 years). The patients were accepted for this study on the premise that their gastrectomy included a systematic lymph node dissection in all 16 JRSGC lymph node stations. The tissue was investigated using the clearing technique mentioned above.

Results

The number of lymph nodes retrieved in the autopsy study varied greatly between individuals as well as in total number in each single station. There were many lymph nodes in stations 3, 12 and 13, and surprisingly few in stations 4, 11 and 15. Only in station 12 were there consistently several lymph nodes in each patient. It is possible to find no lymph nodes at all in all the other stations except 7 and 8 (*Table 2*).

The total number of lymph nodes in groups N_1 and N_2 (i.e. station 1–11) ranged from 17 to 44, the average being 27 (*Figure 1*). When including group N_3 (station 12–16) the average increased to 43 nodes (range 25–64 nodes).

The size of normal lymph nodes varied from station to station (*Table 3*). Nodes along the left gastric artery, common hepatic artery, coeliac artery and in the hepatoduodenal ligament were, on average, double the size of those in other stations. The maximum diameter was 13–22 mm.

In the 36 gastrectomies for cancer, 1273 lymph nodes were removed in stations 1–16, an average of 35·3 nodes (range 9–73 nodes), 363 (28·5 per cent) of which were diseased. In two patients with metastatic involvement of all perigastric lymph

Table 1 *Clinical data of autopsy patients* (n = 30)

Men/women	18/12
Average age (years)	67·6
Reasons for death	
Pulmonary embolus	9
Myocardial infarct	4
Pneumonia	5
Central nervous system upsets	5
Acute myocardial insufficiency	3
Dissecting aortic aneurysm	1
Split of the aortic valve	1
Hypoxia	1
Uraemia	1

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Table 2 *Lymph node count in the upper abdomen*

Station	Location (JRSGC)	Normal values (autopsy study) Average (range)	Control group (R_3 gastrectomies) Average (range)
1	Right side of cardia	2·2 (0–4)	2·1 (0–5)
2	Left side of cardia	2·0 (0–5)	2·0 (0–7)
3	Along lesser curvature	4·5 (0–14)	4·8 (1–16)
4	Along greater curvature	1·2 (0–7)	1·4 (0–7)
5	Suprapyloric, along RGA	2·2 (0–5)	1·8 (0–6)
6	Infrapyloric	2·7 (0–8)	2·7 (0–8)
7 and	Along LGA	4·6 (1–11)	4·5 (0–11)
8	Along CHA		
9	Around CA	4·2 (0–15)	4·2 (0–13)
10	At the splenic hilus	2·2 (0–6)	2·2 (0–7)
11	Along SA	2·0 (0–9)	2·1 (0–6)
12	In hepatoduodenal ligament	5·5 (2–12)	3·2 (0–8)
13	Behind the pancreas head	4·7 (0–11)	3·2 (0–7)
14	At root of mesentery	2·0 (0–7)	1·4 (0–8)
15	Along MCA	0·3 (0–4)	0·1 (0–2)
16	Paraaortic	2·5 (0–8)	1·2 (0–4)
Total			
Station 1–11		27 (17–44)	24 (7–54)
Station 1–16		43 (25–64)	35·3 (9–73)

CA, coeliac artery; CHA, common hepatic artery; LGA, left gastric artery; MCA, middle colic artery; RGA, right gastric artery; SA, splenic artery; SMA, superior mesenteric artery

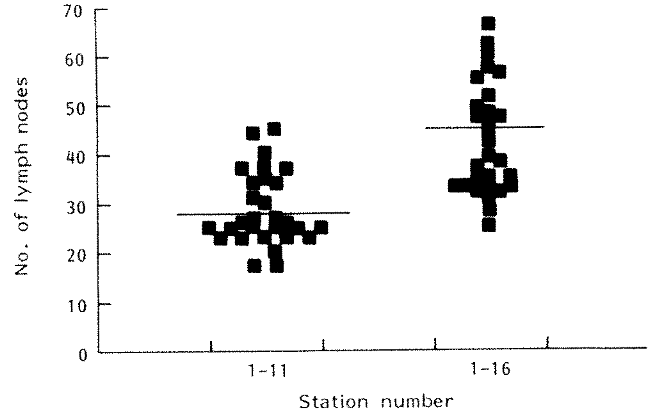

Figure 1 *Results of lymph node dissection in the autopsy study. The average number of nodes in stations 1–11 is 27; this average increases to 43 when the N_3 group of nodes in stations 12–16 is included*

nodes (N_1 group) the count was higher than in the autopsy study, in all 34 other patients the maximum normal values were not exceeded (*Table 2*). The average lymph node size was in almost all stations higher than in the autopsy study group (*Table 3*).

Discussion

The results of the anatomical investigations demonstrate that there are many more lymph nodes in the 16 stations than originally supposed from results obtained at gastrectomy. Soga *et al.*[7] raised the former standard of 30 lymph nodes to 37·9. Siewert *et al.*[8] report 35·4 nodes and by exploring the left pancreas with extirpation of lymph nodes in the perinephric region the value increased to 42·6.

When analysing the anatomical data from non-cancer patients the question has to be addressed as to whether the number of lymph nodes in the upper abdomen is constant. Could the number be abnormally high in patients with cancer?

Table 3 *Diameter of lymph nodes*

Station	Location	Autopsy group Average (max.) in mm	R_3 gastrectomies Average (max.) in mm
1	Right side of cardia	3·4 (11)	4·1 (18)
2	Left side of cardia	3·4 (17)	4·5 (17)
3	Along lesser curvature	3·5 (11)	5·0 (27)
4	Along greater curvature	2·4 (6)	4·0 (25)
5	Suprapyloric, along RGA	2·8 (8)	6·0 (9)
6 and 7	Infrapyloric/ along LGA	3·2 (10)	5·4 (15)
8	Along CHA	6·3 (22)	8·9 (20)
9	Around CA	5·6 (13)	4·7 (11)
10	At splenic hilus	2·9 (12)	4·0 (7)
11	Along SA	3·6 (13)	3·6 (10)
12	In hepatoduodenal ligament	7·0 (20)	6·3 (14)
13	Behind the pancreas	3·8 (12)	6·4 (12)
14	At root of mesentery	3·9 (14)	4·8 (18)
15	Along MCA	3·1 (7)	2·9 (9)
16	Paraaortic	3·1 (13)	5·8 (10)

The minimal size in each station was 1 mm. For abbreviations see *Table 2*

Tiny lymph nodes with a diameter of <1 mm cannot be made visible by the clearing technique. It is, however, possible that these nodes become visible after becoming involved or as a result of reactive hyperplasia thereby increasing the number of visible nodes. This hypothesis is underpinned by reports of Noguchi *et al.*[3], who removed up to 100 lymph nodes in patients with carcinoma. Our own experience in patients with carcinoma is also consistent with this contention; in two gastrectomies with involvement of all perigastric lymph nodes we also found higher values in the N_1 groups than in the autopsy study. These perigastric lymph nodes were always completely extirpated as they were removed *en bloc* with the stomach. N_2 and N_3 nodes of tumour patients, however, always matched those numbers found in the autopsy study. On the other hand, Siewert *et al.*[8] reported that the number of lymph nodes does not change, regardless of tumour stage or the extent of metastasis.

The results of this anatomical study can be taken as a guideline in quality control of lymph node dissection during gastrectomy. We therefore recommend that one obtains an average of at least 27 lymph nodes in a R_2 resection (dissection of groups N_1 and N_2 = station 1–11). This number should increase to 43 when also dissecting lymph nodes of group N_3 (station 12–16; R_3 resection). With lymph node metastasis these numbers can increase further. According to the new TNM classification of IUCC, N_3 lymph nodes are coded as 'M_1 lymph', being equivalent to distant metastases[9]. Because of individual variations, extirpation of <30 lymph nodes in a R_3 resection cannot be judged incomplete and similarly an extirpation of >30–40 lymph nodes cannot be taken as a guarantee of an adequate lymphadenectomy. Quality control is not possible in a single case but may be applied in a comparable group of patients.

The size of normal lymph nodes varies depending on the region. Perigastric lymph nodes and those of group N3 are smaller than lymph nodes near large vessels and this has to be considered when interpreting preoperative ultrasound results. These investigations show that lymph nodes may have a diameter of 1–2 cm without harbouring metastases. Diseased nodes are usually larger and therefore easier to find.

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Clinical significance of the large adrenal mass

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Current clinical teaching indicates that large (>5 cm in diameter) adrenal masses are often malignant. In a retrospective analysis of patients studied between 1977 and 1988 with computed tomography (CT), adrenal scintigraphy, and when available, magnetic resonance imaging (MRI) 45 were found to have adrenal masses greater than 5 cm (range 5–19 cm) in diameter. Thirty were benign (16 phaeochromocytomas, six adrenocortical adenomas, four adrenal cysts, two myelolipomas, an adrenal hematoma and a ganglioneuroma). Of 15 malignant masses, there were seven adrenocortical carcinomas, five adrenal metastases and three adrenal lymphomas. With the exception of the adrenal myelolipomas, cysts, and the ganglioneuroma neither CT nor MRI demonstrated sufficient diagnostic specificity to distinguish benign from malignant lesions. Functional scintigraphy with ^{131}I-6-β-iodomethyl-19-norcholesterol for suspected adrenocortical lesions and ^{131}I-metaiodobenzylguanidine for suspected phaeochromocytomas frequently provided useful information.

The differential diagnosis and optimal management of coincidentally discovered adrenal masses remains a matter of controversy which has been heightened by the availability of high-resolution computed tomography (CT). Abnormalities of adrenal morphology – masses larger than 1 cm in diameter – are found incidentally in approximately 1 per cent of all patients undergoing abdominal CT[1–3] and up to 26 per cent of patients with primary extra-adrenal malignancies have adrenal metastases at autopsy[4]. Adrenal cortical tumours producing syndromes of steroid hormone excess have an estimated incidence of approximately 4 per million per year and are equally divided between adenomas and carcinomas[5]. Phaeochromocytomas occur with an estimated incidence of 1·5 million per year with only 10 per cent being malignant[6]. Reviews of functioning[5,7] and 'incidental'[8] adrenal masses have emphasized the positive correlation between size of the mass and the likelihood of malignancy. Recommended thresholds for surgical exploration have included diameters of 3–3·5 cm (References 1, 2 and 9), 5 cm (Reference 10) and 6 cm (Reference 8). Among 'non-hyperfunctioning', incidental, unilateral adrenal masses size was found to be a poor discriminator of malignancy, with benign masses ranging between 1 cm and 7 cm in diameter and malignant masses between 1·5 cm and 10 cm (Reference 11). In a subgroup of 28 patients with known extra-adrenal malignancies only ten such masses proved to be adrenal metastases[12]. The clinical, radiologic, scintigraphic and pathological characteristics of large adrenal masses (5 cm or greater in diameter), both hyperfunctioning and non-hyperfunctioning, referred to Ann Arbor between 1977 and 1988 have been studied.

Patients and methods

Individuals with unilateral or bilateral adrenal masses 5·0 cm in diameter or larger were identified from the database of patients referred for adrenal scintigraphy with ^{131}I-6-β-iodomethyl-19-norcholesterol (NP-59), 29 cases from a total of 468 studies (1977–1988) or ^{131}I-metaiodobenzylguanidine (MIBG), 16 cases from a total of 52 sporadic intra-adrenal phaeochromocytomas (1981–1988). Adrenal cortical and/or medulla function was evaluated in all cases with some combination of the following measurements: plasma cortisol (basal morning and evening levels, and levels following overnight suppression with oral dexamethasone and/or stimulation with intravenous adrenocorticotrophic hormone (ACTH); 24-h urinary excretion of free cortisol of 17-hydroxycorticosteroids (17-OHCS); plasma aldosterone and renin activity; 24-h urinary aldosterone excretion; plasma androgens (testosterone, androstenedione, dehydroepiandrosterone (DHEA) and DHEA sulphate); 24-h urinary 17-ketosteroid (17-KS) excretion; plasma catecholamines (adrenaline and noradrenaline); and urinary catecholamine and metabolite (vanillylmandelic acid (VMA), metadrenaline and normetadrenaline) excretion.

Computed tomography was performed in 43 of 45 patients using a variety of scanners between 1977 and 1988 including EMI 5005 (EMI Limited, Middlesex, England), Picker 1200 SC (Picker International Wood Dale, Illinois, USA) GE 8800 and 9800 (General Electric Corporation, Milwaukee, Wisconsin, USA). In most instances, 10 mm contiguous sections were obtained through the region of the adrenal glands. Recently MRI was performed in ten of the 45 patients using a Diasonics MT/A (Palatine, Illinois, USA) superconducting magnet operating at 0·35 T. Generally, 10 mm thick contiguous sections were obtained using a variety of non-gated spin-echo sequences (SE 500/28-30 and SE 2000/28-30, 56-60,100)[13]. The relative intensity of each adrenal lesion was compared visually with the liver and then categorized as hypo-, iso- and hyperintense. Scintigraphy was performed with institutional review board approval and with the patients' informed consent. Thyroidal uptake of free ^{131}I-iodide was blocked with oral Lugol's solution or a saturated solution of potassium iodide (SSKI)[14]. When appropriate, adrenocorticotrophic hormone (ACTH)-dependent uptake of the NP-59 by the zona fasciculata/reticularis was suppressed by pretreatment with oral dexamethasone[15]. Scans were obtained 3–7 days after the intravenous administration of 37 MBq(1 mCi) of NP-59 (Reference 13) or 24–72 h after the intravenous administration of 18·5 MBq (0·5 mCi)/1·73 m^2 (maximum, 37 MBq (1·0 mCi)) of ^{131}I-MIBG[16]. Imaging was performed using a wide-field-of-view γ-camera fitted with a high-energy, parallel-hole collimator and interfaced to a dedicated computer. Images were obtained for 20 min or 50 000 counts per view.

The scintigraphic studies were interpreted using criteria previously described[17,18]. In all but three cases, a tissue diagnosis was made by CT-guided fine-needle biopsy, surgery or autopsy. The maximum diameter of the mass was recorded; in patients with bilateral masses, the maximum diameter of the larger mass was used for statistical purposes. Statistical analysis was by Student's t-test and the χ^2 test.

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Results

The 45 patients ranged in age from 22 years to 88 years (median, 53·5 years; mean(s.d.), 54·1(14·9) years). There were 24 men (median age 55·5 years, range 42–74 years) and 21 women (median age 54 years, range 22–88 years). The masses were on the right side in 23 cases, (ten men, 13 women), on the left in 16 (ten men, 6 women) and bilateral in six (four men, two women). The maximum diameter was 19 cm (median, 7·0 cm; mean(s.d.), 8·1(3·4) cm). There was no significant sex difference in the size of the masses. Five patients presented with endocrine dysfunction compatible with adrenocortocal disease, 16 with hypertension as a result of phaeochromocytoma and 24 patients were studied with CT for reasons other than suspected adrenal disease, usually abdominal pain. Of the incidentally discovered unilateral adrenal masses 23 were included in previous reports that focused on the use and efficacy of scintigraphy in the evaluation of the silent mass[11,12].

Pathology (Table 1)

The masses were proved cytologically and/or histologically to be malignant in 15 cases – primary adrenal cortical carcinoma in seven and adrenal metastases in eight – and benign in 27 cases. The remaining three patients declined biopsy or surgery, but their masses remained unchanged on follow-up of 6 months (one case) to 2 years (two cases) and demonstrated a concordant scintigraphic pattern with NP-59 (i.e., uptake of NP-59 was increased on the side of the mass[11]); they were therefore presumed to be benign, adrenocortical adenomas. Malignant masses (mean maximal diameter(s.d.) 9·7(4·0) cm) were larger than benign masses (mean maximal diameter(s.d.) 6·2(1·1) cm; $P=0{\cdot}006$). Similarly, primary adrenocortical carcinomas were significantly larger (11·4(4·2) cm) than cortical adenomas (5·8(1·3) cm, $P=0{\cdot}017$) or phaeochromocytomas (6·9(1·5) cm, $P=0{\cdot}017$). There was no significant difference in size between primary (11·4)(4·2) cm) and metastatic (8·1(3·3) cm) malignant adrenal masses ($P=0{\cdot}11$), but bilateral masses were always metastatic (large-cell bronchogenic carcinoma, two cases; squamous-cell oesophageal carcinoma, one case; diffuse histiocytic lymphoma, three cases). Nine of 38 unilateral masses were malignant. There was no sex difference between the prevalence of benign or malignant masses, or of primary or metastatic malignant masses ($P>0{\cdot}4$).

Clinical features (Table 2)

Most commonly, the adrenal masses were discovered during the staging and evaluation of patients with known, non-adrenal malignancies – bronchogenic carcinoma (four cases), oesophageal carcinoma (two cases), adenocarcinoma of the colon (one case), transitional-cell carcinoma of the bladder (one case), and non-Hodgkin's lymphoma (one case). In none of these patients were the masses associated with any evidence of obvious adrenal dysfunction, and in only one case (case 1, below) was the mass suspected clinically – thus, the masses were 'incidental' in eight of these nine cases. In three of the patients, the adrenal masses were not due to metastases:

Table 1 *Pathological diagnoses*

Pathology	No. of cases	Maximum diameter (cm)		Side
		Median	Range	
Benign:	30	6·0	5·0–8·0	17R, 13L
Cortical adenoma	6*	5·2	5·0–8·0	5R, 1L
Myelolipoma	2	6·8	6·5–7·0	1R, 1L
Cyst	4	6·0	5·0–7·0	1R, 3L
Haematoma	1	8·0	–	1R
Ganglioneuroma†	1	6·0	–	1R
Phaeochromocytoma	16	7·0	5·0–11·0	8R, 8L
Malignant:	15	9·0	5·0–19·0	6R, 3L, 6B
Cortical carcinoma	7	11·0	7·0–19·0	4R, 3L
Metastatic carcinoma	5	6·0	5·0–9·0	2R, 3B
Lymphoma	3	10·0	8·0–15·0	3B
Total	45	7·0	5·0–19·0	23R, 16L, 6B

*Tissue diagnosis not available in three cases – tumours stable on extended follow-up (see text); † Juxta-adrenal tumour; R, right; L, left; B, bilateral

Table 2 *Clinical presentation*

Known extra-adrenal malignancy*		9
Lung (large cell)	4	
Oesophagus (squamous cell)	2	
Colon (adenocarcinoma)	1	
Bladder (transitional cell)	1	
Lymphoma (diffuse histiocytic)	1	
Abdominal pain		10
Hypertension†		22
Primary aldosteronism	2	
Phaeochromocytoma	16	
Adenoma	3	
Cyst	1	
Hyperandrogenism		2
Other*		2
Anaemia, fever (lymphoma)	1	
Adrenal insufficiency (lymphoma)	1	

*CT performed for reasons other than suspected renal disease; † CT performed for suspected adrenal disease (e.g. aldosteronism, phaeochromocytoma) in 18 of the 22 cases

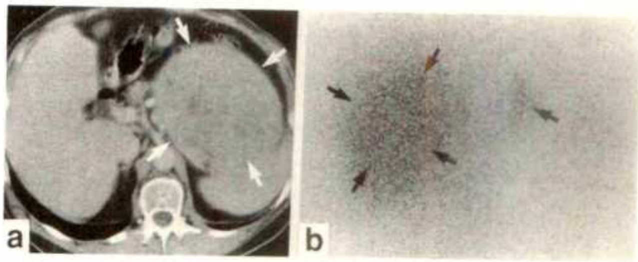

Figure 1 **a** *Abdominal computed tomography scan depicts a large left-sided retroperitoneal mass (arrows) and enlarged periaortic lymph nodes.* **b** *Posterior* ^{131}*I-6-β-iodomethyl-19-norcholesterol scan demonstrates radiotracer uptake in the mass (arrows) and in the normal right adrenal gland (arrow)*

Case 1. A 61-year-old man presented initially with dysphagia and weight loss due to a squamous-cell carcinoma of the oesophagus. A left upper quadrant abdominal mass was noted on clinical examination. A CT scan of the abdomen showed a large, retroperitoneal mass of mixed density with punctate calcifiation, associated with multiple, abnormally enlarged, retroperitoneal lymph nodes (*Figure 1*). The right adrenal gland appeared normal. An NP-59 scan showed extensive uptake on the left consistent with a functioning, but not hyperfunctioning adrenocortical tumour; however, uptake on the right was not suppressed (*Figure 1*). CT-guided fine-needle biopsy of the mass was consistent with adrenocortical carcinoma. At operation, a 19 × 14 × 10 cm, 1175 g, well-differentiated, left adrenocortical carcinoma was removed. Several of the retroperitoneal lymph nodes were biopsied and found to contain metastatic squamous-cell carcinoma – there was no evidence of extra-adrenal spread of the adrenocortical tumour.

Case 2. A 67-year-old man, had a Dukes' stage C carcinoma of the colon resected in 1978. He presented 9 years later with a right abdominal wall mass, which proved to be an abscess. During the evaluation of this mass, a CT scan of the abdomen showed a mixed-density, 7·0 × 6·5 cm right adrenal lesion. The mass was non-functioning on an NP-59 scan. CT-guided fine-needle biopsy yielded only a few lipid droplets, but no cellular material. At laparotomy, a 140 g right adrenal myelolipoma was removed. There was no evidence of metastatic colonic carcinoma.

Case 3. A 66-year-old man, underwent abdominal CT scanning during staging of an invasive, transitional-cell carcioma of the bladder (*Figure 2*). A 5·0 cm right adrenal mass was noted, with a morphologically normal left adrenal gland. An NP-59 scan showed a discordant pattern of imaging, i.e., tracer uptake was reduced on the side of the mass[11]. A CT-guided fine-needle biopsy was unsuccessful. A benign right haemorrhagic adrenal cyst was removed at operation.

In ten patients, the adrenal masses were discovered during the evaluation of abdominal, chest or back pain. The pain could reasonably be attributed to the mass in five of these patients – two with primary adrenocortical carcinoma, two with an adenoma where one was later shown to be autonomously functioning and one with a benign cyst. The initial investigation which disclosed the adrenal mass was plain radiography (one case), intravenous urography (three cases), abdominal ultrasonography (three cases) and CT scanning (three cases). Although none of these patients had clinical evidence of adrenal dysfunction, one (a 35-year-old woman with a 12 × 10 cm left adrenocortical carcinoma with retroperitoneal, pleural and pulmonary metastases) had mildly elevated urinary 17-KS levels (56 μmol/d (reference range: 14–49 μmol/d)) and a second patient (64-year-old man with mild hypertension and emphysema and a 6 cm right adrenal mass) (*Figure 3*) and an elevated urinary free cortisol (284·4 nmol/d (reference range: <140 nmol/d)) and an a.m. plasma cortisol of 248·4 nmol/l (reference range: <138 nmol/l) 12 h after 1 mg of oral dexamethasone. In five patients in whom the pain could not be attributed to the adrenal mass and where there was no evidence of adrenal cortical or medullary dysfunction, the masses could be considered 'incidental'. These were benign (adenoma, cyst, hematoma, myelolipoma, juxta-adrenal ganglioneuroma) lesions.

A total of 22 patients had adrenal masses found in the course of evaluation of hypertension. Of these 16 patients presented with episodic hypertension and headaches and in all elevated plasma and urinary catecholamines and their metabolites were noted. In each case a benign-appearing unilateral, sporadic, intra-adrenal, phaeochromocytoma was found (*Figure 4*). Two patients, who had the typical biochemical features of primary aldosteronism and in whom the masses proved to be functioning adrenocortical carcinomas, have each been the subjects of separate case reports[19,20]; their tumours measured 7 cm and 11 cm in maximal diameter and both neoplasms accumulated NP-59, despite dexamethasone suppression. An additional patient has had intermittent, mild hypokalemia but no evidence of primary aldosteroism, or other biochemical abnormality referable to adrenal cortex or medulla dysfunction. The masses in this group were initially found by intravenous urography in two cases, abdominal ultrasonography in two cases, and by CT scanning in the remaining 18 cases. Apart from the two patients with primary aldosteronism and the 16 cases of phaeochromocytoma, biochemical evaluations were normal. The remaining masses consisted of cortical adenomas (three cases) and a benign adrenal cyst.

Two women presented with symptoms of hyperandrogenism:

Case 4. A 22-year-old woman, presented with hirsutism, secondary amenorrhea, acne and increased libido. Plasma total testosterone (9·5 nmol/l (reference range: 0·84–2·31 nmol/l)) and DHEA sulphate (15·5 μmol/l (reference range: 2·2–7·3 μmol/l)) and urinary 17-KS levels (197·4 μmol/d) were elevated. Urinary free cortisol and 17-OHCS excretion were normal and plasma cortisol suppressed normally following dexamethasone administration. An abdominal CT scan showed a large, partially calcified, right adrenal tumour extending into the inferior vena cava. The affected adrenal could not be visualized with NP-59, while uptake by the left adrenal was normal, a not unexpected circumstance since cortisol and its metabolites were normal. At operation, the tumour was found to extend to the right atrium; a 14 × 13 × 8 cm, 815 g primary adrenal cortical carcinoma was removed via a combined thoracoabdominal approach with cardiopulmonary bypass.

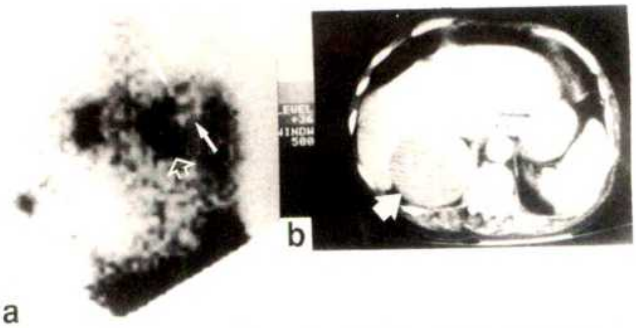

Figure 2 **a** *Posterior* ^{131}*I-6-β-iodomethyl-19-norcholesterol scintiscan depicts a normal left adrenal, a medially displaced right adrenal and a 'cold' area located laterally to the right adrenal (arrow).* **b** *Abdominal computed tomography scan identifies a 5 cm homogenous mass with a calcified rim in the right adrenal area (arrow)*

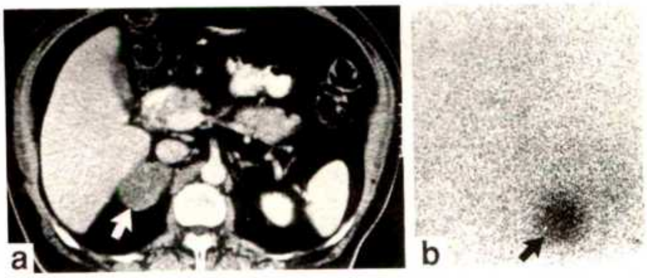

Figure 3 **a** *Abdominal computed tomography scan identified a large (6 cm) right adrenal mass (arrow).* **b** *Posterior chest and upper abdominal* ^{131}*I-6-β-iodomethyl-19-norcholesterol scintiscan depicts a solitary focus of radiotracer uptake that corresponds to a Cushing's adenoma. The contralateral adrenal is not visualized due to suppression of adrenocorticotrophic hormone and* ^{131}*I-6-β-iodomethyl-19-norcholesterol uptake into the normal adrenal*

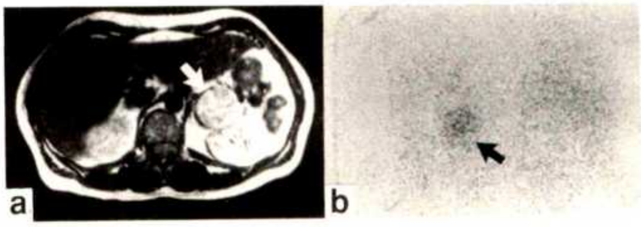

Figure 4 **a** *T2 weighted abdominal magnetic resonance imaging scan of the abdomen of a 67-year-old man with episodic hypertension and elevated plasma catecholamines (E-2019 pmol/l, reference range 0–545 pmol/l, NE-6·86 nmol/l, reference range 0–4·5 noml/l, urinary metenphrine-23·4 μmol/d, reference range $<4·63$ μmol/d, vanillylmandelic acid 53·9 μmol/d, reference range <35 μmol/d) and a 5 cm left adrenal phaeochromocytoma (arrow).* **b** ^{131}*I-metaiodobenzylguanidine scintiscan depicts the neoplasm as a solitary focus of* ^{131}*I uptake in the left abdomen*

Case 5. A 27-year-old woman, presented because of secondary amenorrhea and obesity. She was noted to be mildly hypertensive but had no other clinical stigmata of Cushing's syndrome. Abdominopelvic ultrasonography demonstrated a left adrenal mass, approximately 6·5 cm in diameter. Biochemical evaluation showed elevation of plasma total (5·04 nmol/l (reference range: 0·88–3·33 nmol/l)) and free testosterone (0·98 nmol/l (reference range: 0·11–0·46 nmol/l)), plasma DHEA sulphate (21·2 μmol/l (reference range: 0·84–8·24 μmol/l)), and increased urinary 17-KS excretion (74·9 μmol/d) which failed to suppress (85·1 μmol/d) after high-dose oral dexamethasone. In addition, although plasma cortisol levels and urinary free cortisol and 17-OHCS excretion were normal, there was loss of the normal diurnal variation in plasma cortisol, and urinary free cortisol excretion failed to suppress normally after dexamethasone. A CT scan confirmed a large left adrenal mass with no evidence of extra-adrenal extension (*Figure 5*). An NP-59 scan failed to demonstrate radiopharmaceutical uptake in either adrenal, an expected consequence of autonomous glucocorticoid excess from an adrenocortical carcinoma with suppression of ACTH and contralateral radiotracer accumulation[21] (*Figure 5*). A 7 × 6 × 5 cm, 105 g, primary adrenocortical carcinoma was resected; the patient required glucocorticoid support in the early postoperative period.

The remaining two patients had lymphomas involving the adrenals. A third patient with adrenal involvement by lymphoma has been mentioned among the patients with known extra-adrenal primary malignancies (above):

Case 6. A 53-year-old woman was evaluated in 1982 after treatment for stage IVb diffuse histiocytic lymphoma. In 1986, she presented once again in relapse with clinically bulky abdominal disease. Abdominal CT and MRI scans demonstrated very large, bilateral adrenal masses (maximum diameter 15 cm) where the largest mass (right) was hyperintense and the smaller, (left) was hypointense as compared with liver on a T-2 weighted MRI scan (*Figure 6*). An NP-59 scan demonstrated a small focus of residual cortical activity on the right and no evidence of adrenocortical function on the left (*Figure 6*). CT-guided fine-needle biopsy of the left adrenal mass confirmed lymphomatous involvement. Biochemical evaluation showed no evidence of adrenocortical hormone excess; she had no clinical evidence of glucocorticoid deficiency.

Case 7. A 57-year-old woman, had been extensively investigated for a longstanding anemia and neutropenia. In 1977, she developed fever and weight loss. An ultrasound examination of her abdomen showed a rounded mass below the right lobe of the liver. An abdominal ^{67}gallium citrate scan showed bilateral adrenal uptake of ^{67}gallium citrate, but both adrenals failed to accumulate NP-59[22]. There was no evidence of adrenocortical hypofunction but the possibility of glucocorticoid insufficiency was not formally evaluated. At laparotomy, the patient was found to have diffuse histiocytic lymphoma involving the right adrenal, with widespread retroperitoneal disease. Postoperatively, she suffered recurrent fevers, despite empiric antibiotic therapy, recurrent supraventricular tachyarrhythmias and episodic hypotension, and died approximately 1 week after surgery. At autopsy, widespread retroperitoneal lymphoma was confirmed; the right adrenal (which had been biopsied) measured 7 × 4 × 2 cm and was partially haemorrhagic, and the left measured 8 × 6 × 6 cm. There was no identifiable residual adrenal tissue.

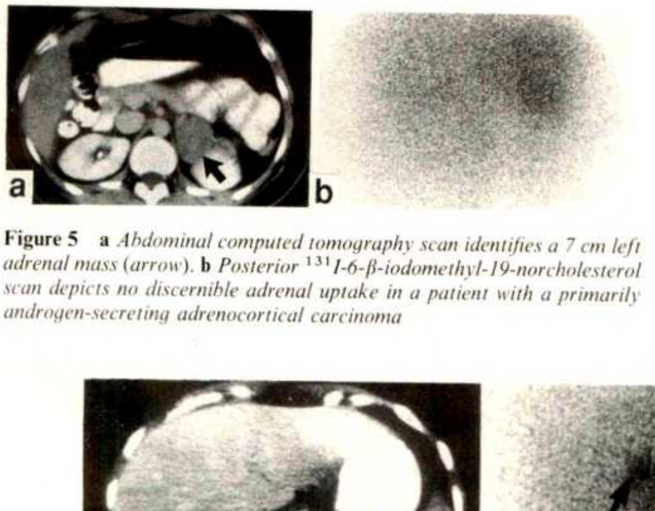

Figure 5 **a** *Abdominal computed tomography scan identifies a 7 cm left adrenal mass (arrow).* **b** *Posterior* ^{131}*I-6-β-iodomethyl-19-norcholesterol scan depicts no discernible adrenal uptake in a patient with a primarily androgen-secreting adrenocortical carcinoma*

Case 8: A 59-year-old man who had been treated for diffuse histiocytic lymphoma in 1984 and was considered to be in remission. In mid-1986 he presented with fever and muscle weakness. There was no evidence of recurrent lymphoma on clinical examination, but he was noted to be deeply tanned and hypotensive. Initial plasma biochemistry was as follows: sodium 131 mmol/l, potassium 8·2 mmol/l, bicarbonate 16 mmol/l, creatinine 371·3 μmol/l and calcium 3·38 μmol/l. Adrenal insufficiency was diagnosed and confirmed by finding subnormal plasma cortisol levels which failed to rise after the administration of ACTH. Appropriate hormone replacement therapy was commenced. A CT scan was not performed on that occasion. He presented again 3 months later with abdominal pain. A CT scan showed bilateral adrenal enlargement (7 cm diameter on the right, 10 cm on the left) as well as multiple intra-abdominal and retroperitoneal lymph nodes and pancreatic enlargement. An NP-59 scan demonstrated bilateral adrenal absence of iodocholesterol uptake. Combination chemotherapy was recommended, but 1 month later the patient developed cerebral lymphoma with leukoencephalopathy.

Prediction of pathology from imaging studies

In 12 of the 15 patients with primary or metastatic adrenal malignancies, one or more of the following features were evident on the imaging studies: associated lymphadenopathy, invasion of the inferior vena cava, bilateral adrenal masses, hepatic or pulmonary metastases, a 'discordant' pattern of imaging between the CT and NP-59 scan[11], and bilateral nonvisualization of the adrenals on the NP-59 scan[11]. Retroperitoneal lymph node enlargement and/or discordant imaging were also present in five of the 13 patients with benign lesions (truly non-functioning and space occupying, e.g. cyst and myelolipoma, masses)[11]. An additional patient had a normal pattern of NP-59 scintigraphy despite the presence of a 6·0 × 5·5 cm mass on the right; she proved to have a juxta-adrenal ganglioneuroma with a normal right adrenal gland. The uptake of iodocholesterol was seen in the adrenal mass of four patients with well differentiated adrenocortical

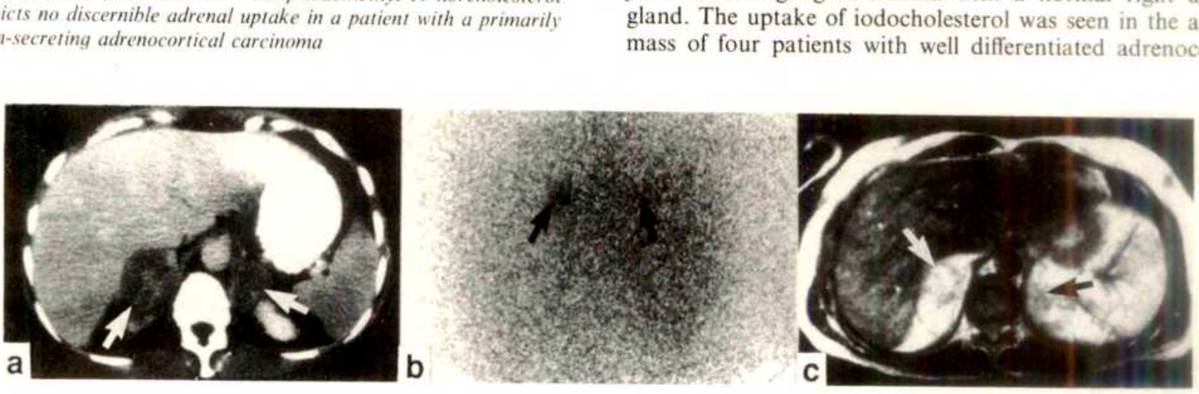

Figure 6 **a** *Abdominal computed tomography (CT) scan demonstrates bilateral adrenal masses, right > left, due to lymphoma (arrows).* **b** ^{131}*I-6-β-iodomethyl-19-norcholesterol scan depicts the adrenal involvement with discernible radiotracer uptake on the left and faint uptake on the right (note the discordance with the CT scan).* **c** *T2 weighted abdominal magnetic resonance imaging (MRI) scan (at the same level as the CT scan) demonstrates the right mass (arrow) as hyperintense and the left (arrow) as more isointense as compared with the MRI signal of the liver*

carcinomas; two with glucocorticoid and two with mineralocorticoid excess. In 16 patients with intra-adrenal, sporadic, non-familial, phaeochromocytomas, ^{131}I-mIBG scintigraphy was successful in identifying all but one case. Magnetic resonance imaging was performed in eight of the cases and successfully identified the abnormal anatomy in all of these cases. CT-guided fine-needle biopsies were performed in 13 patients. Three biopsies were non-diagnostic and no complications of needle biopsy were noted.

Discussion

In this series, patients with large adrenal masses were twice (30/15) as likely to have benign as malignant masses. If only patients with masses larger than 6 cm diameter were selected, as suggested by Copeland[7], the ratio of patients with benign masses to patients with malignant masses would have fallen to 26·6 (Reference 7). Size alone was an imperfect criterion of malignancy but in this selected subgroup of patients with adrenal masses, larger masses were more likely to be malignant (*Table 1*). These data differ from those of Bertanga and Orth where in 58 patients with adrenocortical tumours, 31 had masses greater than 5 cm in diameter and seven were benign while 24 were malignant[23]. In the present study, however, the population included those cases sent for scintigraphy (NP-59 or mIBG) and patients with probable metastatic disease to the adrenals; an anticipated greater proportion of malignant adrenal masses due to the prediliction of the adrenal as a site(s) for metastatic involvement[24].

The adrenal masses were clinically 'silent' or 'incidental' in the majority (64 per cent) of patients – in nine of 11 patients with extra-adrenal malignancies (including two of three patients with lymphoma), five of ten patients with pain, and four of six patients with hypertension. Only six patients had clinical syndromes of adrenocortical dysfunction and five patients had pain which could reasonably be attributed to their tumours and one patient had a palpable abdominal (adrenal) mass.

In patients known to have primary, extra-adrenal malignancies, large adrenal masses do not necessarily represent metastases, especially if unilateral. Whereas the masses were metastatic in eight of the 11 patients with extra-adrenal malignancies, this was true in only two of the five patients with extra-adrenal malignancies and large, *unilateral* adrenal masses. Similarly, in our earlier survey of unilateral adrenal masses greater than 1 cm in diameter – all of which were 'incidental' – among 28 patients with known extra-adrenal primary malignancies, only one-third of the masses proved to be metastases[11]. The distinction is clinically important if an adrenal mass represents the only possible site of metastatic disease found during tumour staging, in which case the nature of the mass must be determined. Four of the eight patients in the present study with adrenal metastases (two unilateral, two bilateral) had large-cell, poorly differentiated bronchogenic carcinoma; neither patient with a unilateral adrenal metastases had any other evidence of extrathoracic metastases.

No combination of imaging modalities could be relied upon to 'prove' the nature of these large adrenal masses. In this series, the usual imaging criteria of malignancy were sensitive (86 per cent) but less specific (75 per cent) but these data include patients with bilateral metastases, a condition in which a normal adrenal is unavailable for scintigraphic comparison rendering scan interpretation more difficult. The bilateral absence of radiocholesterol uptake in a patient with bilateral masses would suggest bilateral metastatic involvement and perhaps adrenal hypofunction[11,22]. The only invariable sign of (metastatic) malignancy was bilateral disease (six of six cases) and these patients had clinical evidence of widespread disease. Among patients with primary adrenocortical tumours, radiological evidence of extracapsular and/or inferior vena cava invasion, and 'bilateral non-visualization' on radiocholesterol scintigraphy are likely to be specific for a hyperfunctioning, large, well-differentiated, adrenocortical carcioma, but only three of our seven patients with adrenal cortical carcinoma had one or more of these signs. Case 1 and the two patients with malignant, well differentiated aldosterone secreting tumours[19] had apparently encapsulated neoplasms on CT scans and sufficient NP-59 for visualization; the 'associated lymphadenopathy' in case 1 proved to be due to metastatic oesophageal carcinoma and the visualization of this mass may be due to its size. This contrasts with our previous experience with the entire spectrum of *non-hyperfunctioning*, but unilateral adrenal masses in which a concordant pattern of NP-59 uptake was invariably associated with benign pathology[11,12]. Although cases of *hyperfunctioning*, well differentiated malignant adrenocortical neoplasms, i.e. glucocorticoid and aldosterone-secreting, have imaged with iodocholesterol and the postoperative course of these patients was more akin to that expected of a patient with a benign neoplasm with subsequent biochemical normalization and cure[20,25]. The ability of a neoplasm to accumulate radiocholesterol appears to be to a large degree dependent upon its state of differentiation; well differentiated malignancies are more likely to accumulate sufficient NP-59 for visualization while less well differentiated lesions are not[21]. The clinical course of such patients can usually be predicted by the presence of NP-59 uptake as these lesions have a different, more benign course[24,25]. Rarely an adrenocortical carcinoma causing Cushing's syndrome may show good uptake of NP-59 and be associated with metastases and one cannot categorically imply a benign course based on a 'positive' scan[25]. Too few of the patients in this series underwent MRI to permit a detailed evaluation of this modality. Its ability to distinguish between benign and malignant adrenal masses has been disappointing in other studies[26,27,28].

None of the patients with adrenal cortical adenomas (four women, two men) had clinical or biochemical evidence of adrenal hyperfunction, although a 6 cm adrenal mass found incidentally in a 63-year-old man presenting with back pain and emphysema was later shown to exhibit autonomous glucocorticoid secretion. All four clinically hyperfunctioning tumours were malignant. The remaining three carcinomas were not clinically hyperfunctioning, although one showed slightly increased urinary 17-KS excretion; the other two patients were men with tumours measuring 10 cm and 19 cm in maximal diameter, neither of whom had clinical evidence of feminization although biochemical evidence of hyperestrogenism was not specifically sought. Thus five of seven 'non-hyperfunctioning', large, primary adrenal tumours were benign. Although large size is considered a reliable criterion of malignancy in functioning, primary adrenocortical tumours[5], it is by no means absolute. Androgen excess cannot be relied upon to make this distinction[5,29,30]. None of the patients with phaeochromocytomas had malignant neoplasms, despite their size, although given the predilection of these tumours to recur at times remote from their original diagnosis and the difficulty in distinguishing benign from malignant tumours on histological criteria alone demands careful long term follow-up and clinical vigilance[6,31,32].

None of the lymphomas in this series arose primarily in the adrenal. All three patients had diffuse histiocytic lymphoma and all had bilateral adrenal involvement. Macroscopic involvement of the adrenals evident on CT scans has been found in 1–4 per cent of patients with non-Hodgkin's lymphoma, with bilateral masses in about half the cases[33]. In case 7, bilateral adrenal uptake of ^{67}gallium citrate together with absent NP-59 uptake was, in the clinical setting, highly suggestive of bilateral adrenal lymphoma. Adrenal ^{67}gallium citrate uptake is not specific for lymphoma[34]. The presentation of case 8 with adrenal insufficiency was the first clue to recurrence of his lymphoma after a 2-year remission; lymphoma presenting with hypoadrenalism is unusual[35]. It is possible, although unproven, that adrenal insufficiency may have contributed to the terminal illness of case 7.

In conclusion, adrenal masses 5·0 cm or more in diameter are frequently but not invariably malignant. The larger the mass, the more likely it is to be malignant, but no clinical, biochemical, radiologic or scintigraphic criteria are inveriably sensitive or specific to enable discrimination between benign and malignant large adrenal masses. In patients with primary extra-adrenal malignancies, bilateral large adrenal masses are highly likely to represent adrenal metastases[36] and other evidence of metastatic disease is usually apparent. In these cases it may be clinically more important to exclude adrenal insufficiency than to pursue the histological diagnosis of the masses[37]. Hyperfunctioning adrenal tumours require surgical treatment regardless of size. Large, non-hyperfunctioning, unilateral masses apparently confined to the adrenal were more likely to be benign (13 of 17 cases) than malignant: application of size recommendations to operate on such masses only if they exceeded 6 cm in diameter would have successfully identified all four malignancies in this series[7]. This study lends further support to such a relatively conservative approch, provided it is applied only in the last, highly selected, subgroup of patients. In the present series, although malignant adrenal masses were encountered more frequently, large benign adrenal masses were still two times more common.

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Success and failure with neonatal tracheo-oesophageal anomalies

In seven and a half years, one surgical team treated 67 consecutive neonates with oesophageal atresia and/or tracheo-oesophageal fistula. According to Waterston's classification, 28 were in group A, 12 in group B and 27 in group C. The mortality rate during the initial admission was 10 per cent, all seven deaths being unavoidable in infants in group C with multiple anomalies. Birthweight alone had no bearing upon the chances of survival. Primary oesophageal repair, including one suture–fistula procedure and one delayed primary repair, was attempted in 54 (84 per cent) of the 64 patients with atresia and was successful in 46 (85 per cent). All three H-type tracheo-oesophageal fistulae were successfully divided in infants in group A. Recurrent tracheo-oesophageal fistula developed in four (7 per cent) infants, one of whom (group A) underwent successful repair. One disrupted anastomosis was successfully resutured (group A), so an intact oesophagus was finally achieved in 51 patients, of whom six (12 per cent) developed anastomotic strictures and 21 (41 per cent) underwent surgery for gastro-oesophageal reflux. Of the 60 early survivors, 10 (17 per cent) underwent aortopexy for tracheomalacia. Whenever possible, primary repair is advocated in all infants. Even for those in group C with multiple, severe associated anomalies, the combined early and late mortality was no greater following primary repair (7 died of 12 operated) than after staged repair (4 died of 7 operated), but major anastomotic complications were more common in infants in group C (5 out of 19) than in those in groups A and B (3 out of 38).

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Numerous papers have been written about various aspects of oesophageal anomalies and their treatment, but results of personal series have rarely been published. Most papers have concentrated on survival rates and few have given success rates for attempted anastomosis.

Patients and methods

Between December 1980 and July 1988, 67 consecutive neonates, 41 boys and 26 girls (male:female ratio 1·6:1), with oesophageal atresia and/or tracheo-oesophageal fistula were treated by one paediatric surgical team. All operations were performed in the presence of the senior surgeon. All case records were reviewed and the results analysed.

The incidences of the various types of oesophageal defect were recorded (*Table 1*). The patients were classified according to Waterston *et al.*'s[1] criteria, 28 being in group A, 12 in group B and 27 in group C. The majority (81 per cent) had the common variety of oesophageal atresia with distal tracheo-oesophageal fistula. Two infants had oesophageal atresia with obliterated distal tracheo-oesophageal fistula[2].

A total of 118 associated anomalies were detected in 50 (75 per cent) patients (*Table 2*), 9 per cent having serious genetic defects. Of the anorectal anomalies, six were high, five low and one intermediate. The most common cardiac lesions were ventriculoseptal defects and patent ductus arteriosus. The most common gastrointestinal anomalies were intestinal malrotation (36 per cent), pyloric stenosis (9 per cent) Meckel's diverticulum (9 per cent) and ectopic pancreas (6 per cent).

Primary repair was attempted in 57 patients (including one delayed primary repair, one suture–fistula operation[3,4], and three repairs of H-type fistula). Thoracotomy was performed through the triangle of auscultation in 50 patients, using an extrapleural approach in most. All anastmoses, except that arising from the suture–fistula procedure, were constructed using a single layer of interrupted 00000 polyglycolic acid. Neither Haight anastomosis nor the Sulamaa–Duhamel–Beardmore procedure was used[5]. Three patients had successful primary oesophageal anastomosis using a combined thoracic and cervical approach[6]. Circular myotomy was never used[6,7]. Gastrostomy was avoided whenever possible but nearly all infants had a small bore transanastomotic Silastic (Dow Corning, Reading, UK) nasogastric tube passed for early postoperative feeding[8].

Postoperatively all patients underwent upper gastrointestinal radiological studies for gastro-oesophageal reflux and the majority underwent tracheobronchoscopy to exclude recurrent tracheo-oesophageal fistula and tracheomalacia.

One patient with congenital diaphragmatic hernia did not undergo oesophageal surgery and nine had staged procedures. Mechanical ventilation was required by 33 (49 per cent) infants: the one with a diaphragmatic hernia, five of the nine undergoing staged repair, all three with an H-type fistula, and 24 (44 per cent) of those undergoing primary repair (6 out of 24 in group A, 4 out of 11 in group B, and 14 out of 19 in group C).

Table 1 *Classification of infants according to type of oesophageal anomaly**

Type of anomaly	Number of patients	Percentage of patients
Oesophageal atresia with distal fistula (type a)	54	81
Oesophageal atresia with proximal and distal fistula (type e)	4	6
H-type tracheoesophageal fistula (type f)	3	4
Oesophageal atresia, without fistula (type c)	2	3
Oesophageal atresia with proximal but no distal fistula (type d)	2	3
Oesophageal atresia with obliterated distal fistula (type b)	2	3
Total	67	100

* The typing system follows that of Waterston *et al*[1]

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Table 2 *Associated anomalies present in 50 (75 per cent) of the 67 patients**

	Number of anomalies	Percentage of patients
Gastrointestinal	41	62
Skeletal	30	45
Cardiovascular	18	27
Anorectal	12	18
Genitourinary	9	13
Genetic	6	9
Congenital diaphragmatic hernia	1	2
Congenital toxoplasmosis	1	2
Total	118	

* Many patients had several associated anomalies

Table 3 *Survival rates* according to Waterston* et al *'s risk groups*[1]

Group	Number of patients	Early survivors*	Late survivors*
A	28 (42)	28 (100)	27 (96)
B	12 (18)	12 (100)	12 (100)
C	27 (40)	20 (74)	15 (56)
Total	67 (100)	60 (90)	54 (81)

* Early survivors were those surviving initial admission, whereas late survivors are those alive at the time of writing this paper. Numbers in parentheses are percentages

Results

There were seven early and five late deaths in infants in group C (56 per cent survival), no deaths in group B, and one late 'cot death' in group A (*Table 3*). Except for the last infant, all had major associated anomalies and four of those dying early in group C had serious chromosomal abnormalities. The 13 deaths were analysed in greater detail (*Table 4* and *Table 5*). None of the early deaths was preventable and none was caused solely by surgical complications.

Except for one neonate with pure atresia, all infants in group A have an intact oesophagus. In group B one infant with cleft lip and palate had an upper pouch fistula but no distal oesophagus, and required colon interposition. All other infants in group B retain the oesophagus except for one with long gap atresia who underwent Gough flap repair[9,10] and developed a recurrent tracheo-oesophageal fistula necessitating emergency oesophagostomy and gastrostomy.

In group C, division into groups C1 (9 out of 13 alive) and C2 (6 out of 14 alive) according to Waterston *et al.*[1], was less helpful as a prognostic exercise than division into two groups according to the presence or absence of severe associated anomalies regardless of birthweight. There were no serious associated anomalies in seven infants weighing less than 1·8 kg, all of whom survived primary repair, although two subsequently had the oesophagus abandoned because of recurrent tracheo-oesophageal fistula. Multiple severe abnormalities were present in 20 infants of various weights, seven of whom died early (three primary repairs, three staged repairs and one diaphragmatic hernia with an untreated oesophagus) and five died late (four

Table 4 *Associated anomalies and cause of death in seven patients dying during initial admission (all in Waterston's group C)*

Birthweight (kg)	Initial treatment	Associated anomalies	Cause of death
4	Primary repair	Down's syndrome, PDA, absent coronary sinus	CCF
2·5	Oesophagostomy, gastrostomy	Down's syndrome, VSD, truncus arteriosus	CCF
1·65	Primary repair	VATER, PDA, ileal atresia, hydrocephalus	BPD plus anastomotic leak
1·57	Oesophagostomy, gastrostomy	CHARGE association	CCF
1·4	No oesophageal surgery	Repaired congenital diaphragmatic hernia	Pulmonary hypoplasia
1·4	Oesophagostomy, gastrostomy	Trisomy 18	
1·3	Primary repair	Trisomy 17, severe cleft lip and palate	Failure of spontaneous respiration from birth plus anastomotic leak

PDA, Patent ductus arteriosus; VSD, ventriculoseptal defect, BPD, bronchopulmonary dysplasia; CCF, congestive cardiac failure; VATER, Vertebral, Anorectal, TracheoEsophageal, Radial, Renal association; CHARGE, Coloboma, Heart disease, Atresia choanae, growth and development Retardation, Genital hypoplasia and Ear anomalies association

Table 5 *Associated anomalies and cause of late death in six patients surviving the initial admission*

Birthweight (kg)	Initial operation	Associated anomalies	Cause of death
3·3	Primary repair	G Syndrome: laryngopharyngeal cleft, hypospadias	Intestinal adhesion obstruction (treated elsewhere)
3·1	Primary repair	VATER	Gram-negative shock: urinary tract infection
2·83	Primary repair	Epilepsy, retardation, talipes, congenital dislocation of hip	Congenital toxoplasmosis, respiratory failure requiring mechanical ventilation from birth
2·52	Oesophagostomy, gastrostomy	Anorectal agenesis, pyloric stenosis	Perforation of oesophageal stricture
2·36	Primary repair	VATER	Asystole after VSD repair
2·5*	Primary repair	None	'Cot death'

VSD, Ventriculoseptal defect; G syndrome, Opitz–Frias dysphagia-hypospadias syndrome with hypertelorism and oesophageal anomaly. affects males and partial expression in female carriers. The aetiology is unknown. variable patterns of inheritance * Waterston's group A· all other infants were in Waterston's group C primary repairs, one staged repair). Only four (20 per cent) infants in group C with multiple anomalies survived with an intact oesophagus.

Of the 57 primary repairs (group A, $n=27$, including 3 H-type fistulae; group B, $n=11$; group C, $n=19$), 49 (86 per cent) were successful at the first operation. One anastomosis (group A) disrupted but was successfully resutured. The tracheo-oesophageal fistula recurred in four (7 per cent) infants. In one infant (group A) the recurrent tracheo-oesophageal fistula was successfully sutured, but in three (one in group B, two in group C) the oesophagus had to be abandoned with temporary oesophagostomy and gastrostomy prior to successful gastric interposition. The anastomosis partially disrupted in two infants in group C and, despite oesophagostomy and gastrostomy, both eventually died, one with trisomy 17 and the other from bronchopulmonary dysplasia and hydrocephalus (*Table 4*) One infant (group C) with multiple anomalies underwent delayed primary repair of long gap atresia, resulting in anastomotic disruption requiring gastric interposition.

Of the nine patients undergoing staged treatment, two had pure oesophageal atresia, two had oesophageal atresia with a short upper pouch and upper pouch fistula, one had oesophageal atresia with an obliterated distal tracheo-oesophageal fistula, and four had the common type of oesophageal atresia with a distal fistula but with a short upper pouch producing a long gap between the oesophageal segments. One of these last underwent ligation and division of the distal tracheo-oesophageal fistula without any attempt at oesophageal anastomosis but nevertheless developed recurrence of the fistula necessitating reoperation. Three patients died before oesophageal replacement could be performed. Each of these had serious associated chromosomal abnormalities (*Table 4*) or the VATER[5] or CHARGE[11] association. Oesophageal replacement was performed in six cases with colon (one patient) or gastric interposition (five patients). Late preventable death from tension pneumothorax after dilatation of the oesophagogastric anastomotic stricture occurred in one of the five infants undergoing gastric interpositions[12].

Aortopexy for severe, life-threatening tracheomalacia was performed in 10 (17 per cent) of the 60 initial survivors[13] Nissen fundoplication for severe, persistent gastro-oesophageal reflux was performed in 21 patients (41 per cent of the 51 with an intact oesophagus).

Discussion

The survival rates of infants with oesophageal atresia have gradually improved over the last 40 years[1,5,8,13–19] despite the fact that during the last decade the number of infants of low birthweight referred for surgery seems to have increased[20–22]. In this series none of the infants in Waterston's[1] groups A or B died after surgery but one infant in group A subsequently suffered a 'cot death'. With this exception, death occurred only in infants with prenatal infection, chromosomal abnormality, CHARGE or VATER association, or other severe associated congenital defects, especially of the heart[17–19].

In group C infants, the gap between the oesophageal ends is often long, rendering primary repair difficult and fraught with complications[18,19]. As a result, staged repair has been advocated for this group[1,5,17]. In the seven group C infants undergoing staged repair in our series, there were three early unpreventable deaths (*Table 4*). After repair under tension, anastomotic dehiscence and recurrence of the tracheo-oesophageal fistula occur with undue frequency and our initial mortality rate for infants so treated was 16 per cent although all three deaths resulted mainly from associated anomalies. Our present practice is to try to effect primary repair in all patients in whom both ends of the oesophagus are in the chest and to ventilate electively those in whom we consider that the oesophagus has been repaired under tension, as advocated by Rickham[23] and McKinlay and Burtles[24]. We believe that whereas the best oesophagus is produced by joining together the segments with which the infants has been provided, effort should not be wasted in trying to drag together the two widely separated ends of the oesophagus in sickly infants with multiple congenital anomalies. In these infants delayed primary repair is expensive and associated with appreciable mortality and we consider that lower morbidity and mortality result from oesophagostomy and gastrostomy followed by either colon or gastric interposition performed through a mediastinal route[12,14,20,24–27].

The initial survival rate of 74 per cent for infants in group C was superficially impressive but five late deaths, at least three of which were preventable, progressively reduced the survival rate to only 56 per cent, a pattern found in other series[15,17,22,23,25,26] Because of their multiple anomalies, requiring numerous risky operations, infants with CHARGE or VATER association have a poor prognosis[11,28,29].

As in other recent reports[8,20,23,25,26], regardless of the Waterston's group, immediate primary repair was attempted in all patients with a distal tracheo-oesophageal fistula and upper pouch extending into the thorax; the only exceptions were infants with severe hyaline membrane disease, extensive pneumonia, severe cyanotic heart disease or diaphragmatic hernia. Primary repair of the oesophagus was successfully achieved by one operation in 73 per cent of patients overall and in 86 per cent of those in whom repair was attempted. With one notable exception[20], the incidence of success in other series is difficult to ascertain and may vary from 50 per cent to 80 per cent[16,18,22,24,25]

Partial anastomotic dehiscence, accompanied by recurrence of tracheo-oesophageal fistula, developed in four cases (7 per cent) and was successfully repaired in one infant in group A. The other symptomatic recurrences developed during the first 2 postoperative weeks in small infants (all weighing less than 2 kg) having primary anastomoses constructed under tension, and in each case the oesophagus had to be abandoned in order to secure adequate ventilation[18]. All three of these infants survived and went on to undergo oesophageal replacement by way of gastric interposition[12,27]. The recurrence rate of 7 per cent for tracheo-oesophageal fistula is an average incidence[8,14,26] and there is no doubt that, whenever the general condition of the infant allows, surgical treatment of the tracheo-oesophageal fistula should be delayed for at least 2 months[5].

Of those undergoing oesophageal repair, 12 per cent (six patients) developed anastomotic stricture. This low incidence we attribute to the use of absorbable polyglycolic acid sutures, the early aggressive prevention of gastro-oesophageal reflux and the fact that we do not routinely endoscope our patients before they go home. Resection of the anastomosis was not required by any of our patients and none underwent repeated oesophageal dilatation; again we attribute this to early anti-reflux surgery, all strictures resolving after such surgery[30,31].

An anti-reflux operation was performed in 41 per cent (21 patients) of those with an intact oesophagus. This is a very high incidence for an European series but is not excessive by recent North American standards[8,14,18,32,33]. Unlike some authors[20,34,35], we are unimpressed by the results of medical treatment of symptomatic gastro-oesophageal reflux in association with oesophageal atresia in infants over 6 months old. Our experience has been that such reflux may persist for years[30,31,35,36] and that most symptomatic infants with reasonable distal oesophageal peristalsis respond well to early fundoplication[17,37]. Fundoplication in the absence of distal oesophageal peristalsis may result in dysphagia necessitating temporary feeding gastrostomy, as was required by one of our patients[38]. Some of the children in our series also underwent Ladd's procedure for intestinal malrotation and excision of Meckel's diverticulum[22,39,40]. It might be that the teratogenic factor which caused oesophageal atresia also resulted in delayed return into the abdominal cavity of the midgut loop from the physiological umbilical hernia of the fetus, predisposing to the intestinal anomalies and to the subsequent development of gastro-oesophageal reflux. The high incidence of ectopic pancreatic tissue in these infants is difficult to explain[40]. After operation, only one of the patients undergoing anti-reflux surgery has required repeated hospitalization for recurrent chest infections, which are often associated with nocturnal regurgitation[32,38,41].

Aortopexy for tracheomalacia was performed in 17 per cent of the early survivors, a relatively high incidence[13]. Up to a decade ago many patients died unexpectedly during recurrent apnoeic attacks associated with either gastro-oesophageal reflux or tracheomalacia, and a combination of the two is particularly sinister[13,16,17,22,25,26,31,41,42]. In this series the only death from Waterston's group A or B occurred at home in an infant aged 6 weeks and was attributed to 'cot death', but we suspect that it was a consequence of tracheomalacia and/or gastro-oesophageal reflux.

All infants with an intact oesophagus feed well by mouth and significant dysphagia is experienced by only two survivors, one of whom has distal oesophageal dysmotility following a successful suture–fistula procedure. The other has a gastric interposition following an unsuccessful delayed primary repair for long gap atresia. None has been readmitted for removal of an impacted food bolus[18].

In most neonatal surgical units, infants with oesophageal atresia in Waterston's groups A and B are no longer a surgical challenge. Low birthweight infants without multiple serious associated anomalies tolerate primary repair well, but elective postoperative mechanical ventilation should be considered. Surgery of infants with multiple congenital anomalies remains problematic: primary repair should be attempted only when the two ends of the oesophagus can be approximated with ease; elective postoperative ventilation is usually required. If the safety of oesophageal anastomosis is in doubt, oesophagostomy and gastrostomy should be performed[1].

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Necrotizing fasciitis

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Ten cases of necrotizing fasciitis are reviewed. Three patients died but only two of these deaths were due to uncontrolled septicaemia. All isolated organisms were sensitive to a combination of piperacillin and ampicillin which we now regard as the initial antibiotic combination of choice. Prompt and aggressive surgical debridement remains the cornerstone of management.

Necrotizing fasciitis is a term coined by Wilson in 1952 to describe a rapidly progressive inflammation and necrosis of subcutaneous tissue, superficial fascia and superficial part of the deep fascia with secondary necrosis of the overlying skin[1]. It replaced the old nomenclature of haemolytic streptococcal gangrene, Meleney's ulcer and acute dermal gangrene. It is caused by a mixed growth of aerobic and anaerobic organisms. An underlying systemic illness such as diabetes mellitus or malignant disease, or the use of immunosuppressive therapy may predispose to and/or serve as an aggravating factor in those who are affected. The disease carries a high rate of morbidity and mortality especially in the elderly.

Necrotizing fasciitis is uncommon. We have encountered ten cases over the last 5 years in our department. Awareness of the presence of this clinical entity is essential in order to implement therapy early and efficiently.

Patients and methods

Ten patients with necrotizing fasciitis were diagnosed and managed in the Department of Surgery, Amiri Teaching Hospital, Kuwait during the period 1985–1989. *Table 1* summarizes the clinical data and course of these patients. The mean age of presentation was 53·8 years (range 25–83 years). Most of the patients presented late (more than 5 days) after the onset of the condition.

A predisposing cause was found in every case. Diabetes mellitus was the underlying cause and/or aggravating factor in eight of the cases. In addition, four patients (cases 5, 6, 9 and 10) had chronic renal failure as a complication of diabetes mellitus and atherosclerosis.

Once necrotizing fasciitis had been suspected the following principles were adopted:

Antibiotic therapy

Intravenous antibiotics to cover a wide spectrum of organisms were started immediately. Cefuroxime, metronidazole and crystalline penicillin were used initially until a change was necessitated by the results of culture.

Major debridement

Emergency aggressive and extensive debridement of all necrotic tissue (skin, subcutaneous tissue and fascia) was carried out until healthy bleeding tissue was reached. The wound was thoroughly washed with hydrogen peroxide (H_2O_2) and saline, and then dressed with H_2O_2 soaked packs. Excised tissues were sent for histopathological examination and culture.

After not less than 12 h the wound was inspected (under general anaesthesia in the operating theatre) and further debridement carried

Table 1 *Clinical data of ten patients with necrotizing fasciitis*

Patient	Age (years)	Sex	Duration of symptoms (days)	Predisposing factors	Site	No. of major debridements	Hospital stay (days)	Complete healing (days)	Outcome
1	52	M	6	Perianal abscess Diabetes mellitus	Perineum, lower scrotum	2	33	73	Recovered
2	25	M	9	Perianal abscess	Perineum, lower scrotum	2	28	75	Recovered
3	46	M	4	Perianal abscess	Perineum, lower scrotum	2	26	45	Recovered
4	58	M	4	Diabetes mellitus	Perineum, scrotum	3	74	22	Recovered
5	58	M	7	Chronic renal failure Diabetes mellitus	Penis, scrotum	Refused amputation of penis	(25)	–	Died
6	54	M	5	Balanitis	Penis	1 partial amputation	(2)	–	Died
7	83	M	15	Adenocarcinoma of sigmoid colon perforated through anterior abdominal wall	Anterior abdominal wall (left inguinal region)	3	(30)	–	Died
8	52	F	3	Diabetes mellitus	Mons pubis	1	9	24	Recovered
9	50	F	15	Chronic renal failure Diabetes mellitus	Right lumbar region	2	38	90	Recovered
10	60	F	2	Diabetic foot infection Ischaemia both legs Chronic renal failure	Thigh and calf	1	24		Discharged against medical advice

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out. Most of the wounds required two or more major debridement procedures except case no. 8 where the area of the necrosis was limited and case no. 10 who refused further debridement and discharged herself against medical advice (*Table 1*).

Minor debridement

During the hospital stay all wounds required further necrosectomies at the bedside under analgesia This was repeated until the wound started to granulate with no trace of necrosis All wounds had to be dressed at least three times a day with washing with chlorhexidine and H_2O_2 followed by packing Hydrogen peroxide soaked gauze was used initially until there was no more necrotic tissue when saline soaked gauze only was applied.

Results

Clinical course (*Table 1*): the mean hospital stay was 29 days (range 2–74 days) and the mean time for complete healing was 54·8 days (22–90 days). There were three deaths, two of which (cases 5 and 6) were due to severe uncontrolled septicaemia. Both patients were very ill and presented late with severe local disease superimposed on diabetes mellitus and chronic renal failure. The third death occurred suddenly in the ward and was probably due to pulmonary embolism (post mortem examination was not performed). At the time of death the patient had recovered from septicaemia and the wound looked clean with healthy granulation tissue.

Case no. 10 was diagnosed early, presenting with pain in the left calf and medial aspect of the thigh in association with blistering and bullae in the calf and dorsum of the foot. At emergency surgery, necrosis was found to involve the skin and subcutaneous tissue sparing only the deep fascia. All necrotic skin and subcutaneous tissue were excised leaving the wounds open for daily dressing and further assessment After 5 days, the wounds in the calf and thigh appeared clean, and a few interrupted loose sutures were applied to approximate the skin edges. Two weeks after the major debridement, the skin edges around the wounds became necrotic. Further excision was offered but the patient refused and discharged herself against medical advice.

Table 2 *Organisms isolated from the ten patients*

	Patients									
Organisms	1	2	3	4	5	6	7	8	9	10
Aerobic										
Escherichia coli	+	+	+	+	+		+			
Proteus species		+				+				
Klebsiella species			+	+		+			+	
Pseudomonas species										+
Enterococci	+			+	+					+
Anaerobic										
Bacteroides	+	+	+	+				+	+	
Anaerobic streptococci	+		+	+		+		+	+	
Total	4	3	4	5	2	3	1	2	3	2

Table 2 lists the organisms cultured from the wounds The mean number of organisms grown per wound was three (range 1–5). Six of the wounds were infected with three or more organisms and seven of the ten wounds showed growth of anaerobic organisms on culture. The most common organisms were *Escherichia coli*, *Bacteroides* and anaerobic streptococci. Each was present in six of the ten cultures, whereas enterococci and *Klebsiella* were present in four of the cases. The antibiotic sensitivity (*Table 3*) showed that all isolated organisms were sensitive to piperacillin except the enterococci.

Discussion

In 1924 Meleny described skin gangrene subsequent to an infective process in the subcutaneous tissue due to haemolytic streptococci[2]. In the same year Cullen described 'postoperative progressive bacterial synergistic gangrene'[3]. As more cases were described and different organisms were found to be the culprits, the term 'necrotizing fasciitis' was introduced by Wilson in 1952[1].

The bacteriology of the lesion has varied widely in reports in the literature and has changed over the years[4–8]. A variety of synergistically acting organisms have been cultured but no specific combination has been found to be associated with this disease entity. This multimicrobial aetiology was also apparent in our ten patients. A serious underlying systemic disease which gives rise to immunocompromise has been reported in up to 90 per cent of patients[7], a contention which is in accordance with our own findings. Eight of our ten patients were diabetic, and four had complications of this disease.

Necrotizing fasciitis may start spontaneously or after minor abrasion injury to the skin The trunk, especially the lower abdomen and perineum, are the most commonly affected sites. The early manifestations of the disease are sudden onset of pain, oedema and redness of the skin which may be overlooked as a simple case of local cellulitis. However, necrotizing fasciitis rapidly progresses to severe local sepsis associated with a dusky discoloration and local blistering of the skin In addition, severe toxaemia and fever develop and are usually out of proportion to the local signs. Furthermore the presence of bullae over a painful area in skin which otherwise appears normal does signify the presence of subcutaneous necrosis. Such findings should call for immediate intervention before the condition progresses further[9]. Moreover, the wounds of such cases should not be closed early as was done in one of our patients (no 10) because further areas of skin necrosis may become manifest later in the course of the disease. The key to the management of these patients is immediate, extensive and aggressive surgical debridement of all necrotic tissue. Simultaneous intravenous fluid therapy and systemic broad spectrum antibiotics should be commenced and systemic ailments such as diabetes should be dealt with.

In our ten patients most organisms were sensitive to piperacillin. It seems appropriate, therefore, to start all cases in which necrotizing fasciitis is suspected on piperacillin and ampicillin therapy until culture sensitivity results become available. The antibiotic combination is relatively safe and non-toxic to the kidneys, and is a reasonable substitute to the use of multiple potentially toxic antibiotics.

Table 3 *Antibiotic sensitivity of isolated organisms*

Organisms	Penicillin	Ampicillin	Co-trimoxazole	Gentamicin	Piperacillin	Cephalosporin	Metronidazole
Escherichia coli		+	+	+	+	+	
Proteus species		+	+	+	+	+	
Klebsiella species			+	+	+	+	
Pseudomonas species				+	+		
Enterococci	+	+					
Anaerobic streptococci	+				+		
Bacteriodes					+		+

In spite of our aggressive early surgical debridement and subsequent necrotectomies our mortality rate was 30 per cent. However, only one of the three deaths was due to uncontrollable septicaemia, while the second patient refused further debridement and the third died suddenly (probably from pulmonary embolism) after the sepsis was under control. Necrotizing fasciitis carries a high morbidity rate and the reported mortality rate is between 70 per cent and 80 per cent in some reports[10,11] and 30 per cent and 40 per cent in others[4,6]. The role of hyperbaric oxygen therapy in the management of this condition is not yet clear and survival rates have varied[8]. Surgical debridement remains the uncontested primary form of management We emphasize the importance of early diagnosis, immediate radical debridement, and appropriate antibiotic cover.

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Effect of fibrin glues on the mechanical properties of healing wounds

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Tissue glues are important in clinical practice. Fibrin based glues have many advantages over non-biological adhesives. The optimum formulation of these glues measured by their effect on mechanical properties of healing wounds has not been determined. Using a model involving standard dorsal skin incisions in adult male Wistar rats various glue formulations were compared by varying the fibrinogen, thrombin and factor XIII concentrations. Calcium (40 μmol/ml) and aprotinin (3000 kallidinogenase inactivator units, KIu/ml) concentrations were kept constant. Animals were killed at 8 days and wounds excised. Standard strips of these wounds were mechanically tested using an Instron tensiometer and the stress, strain, elasticity and work required to rupture wounds were calculated. Results indicate that a fibrin glue with a fibrinogen concentration of approximately 39 g/l and a thrombin concentration of 200–600 units/ml with no added factor XIII will result in wounds with significantly increased stress, energy absorption and elasticity values.

Tissue adhesives have important applications in clinical practice. The main advantages of fibrin based glues over other types include their tissue compatibility, biodegradability and efficacy when applied to wet surfaces. As the fibrinogen component of all the commercially available biological glues is derived from pooled human plasma, these products carry the risk of transmission of viral disease, particularly non-A non-B hepatitis. This concern led to a collaborative project between the Scottish National Blood Transfusion Service (SNBTS) and the Department of Surgery of the University of Dundee for the development of a product examining viral inactivation and formulation. Viral inactivation was carried out at the Protein Fractionation Centre of the SNBTS by a process of dry heat resulting in lyophilized products which retain biological activity[1]. To produce a formulation of glue components (fibrinogen, thrombin, factor XIII, calcium chloride and aprotinin) the constituents of available glues were reviewed The calcium concentration was the same in all preparations. Other constituents showed considerable variation between products (*Table 1*) and indicated the need for studies designed to ascertain the influence of changes in the formulation of the glue on its performance and biological activity. This study examines the effect of varying concentrations of fibrinogen, thrombin and factor XIII on the healing of a skin wound model in the rat.

Materials and methods

For each different glue formulation the concentration of calcium (40 μmol/ml) and aprotinin (3000 KIu/ml) were kept constant. The concentrations of fibrinogen (58 g/l, 39 g/l, 29 g/l, 23 g/l), thrombin (1000 units/ml, 600 units/ml, 200 units/ml, 50 units/ml) and added factor XIII (12 5 units/ml, 6 0 units/ml, 1 0 units/ml) were varied in different experiments and the factor XIII/fibrinogen ratio varied from 0·24 to 0·16

The wound model used to test the biological effect of different glue formulations consisted of 2 cm dorsal skin incisions (three, 3 cm apart) at right angles to the midline in adult male Wistar rats. Anaesthesia was induced and maintained with intraperitoneal pentobarbitone The dorsum of the animal was shaved and, under clean conditions the skin, fat and panniculus carnosus were incised The wounds were randomly assigned to closure with tape alone (Steristrips, 3M Company, Minnesota, USA) or glue and tape. In the latter group 0·2 ml of glue was used in each wound The animals were allowed free access to food (laboratory chow) and drink during the perioperative period The rats were killed at 8 days by placement in an ether jar. The wounds were immediately excised, wrapped in aluminium foil and stored at −70°C (for 1 week) until mechanical testing. Preliminary experiments had shown that there was no significant difference in the mechanical properties of wounds tested fresh and after storage at −70°C for 1 week

Mechanical properties of the wounds

Each wound was thawed at room temperature for 20 min, cut into strips of approximately square cross-sectional area and the width and thickness were measured (cross-sectional area, *A* – *Figure 1*) These measurements were carried out with precision calipers by the same person (D J B). The strips were loaded on to an Instron tensiometer (model 1026, Instron Ltd., High Wycombe, UK) and held between compressed air clamps (10 mm of wound tissue being held in each clamp), with a gauge length (ℓ – *Figure 1*) of 10 mm. These wound strip dimensions were adequate as the wound strength at 8 days was poor. The volume of the specimen (*vol*) was calculated A distracting force was placed on the wound as the crosshead of the tensiometer (carrying one end of the wound strip) moved away from the fixed clamp (carrying the other end of the wound strip) at a constant speed of 50 mm/min This was recorded on a pen and chart recorder as a load–extension curve The force necessary to rupture the wound (*F*), the amount of stretching before rupture (*e*) and the total work done to rupture (*WD*) was measured from the load–extension curve

Table 1 *Concentration of constituents in presently available fibrin glues*

Fibrin glue	Fibrinogen (g/l)	Thrombin (units/ml)	Factor XIII (units/ml)
Tisseel (Immuno Ltd , Vienna, Austria)	≥75	400–500	≥10
Beriplast P (Behringwerke AG, Marburg, West Germany)	65–115	400–600	40–80
Lille (CNTS Fractionation Centre, Lille, France)	90–95	?	25
Transglutine (CNTS Fractionation Centre, Strasbourg, France)	≥70	200	?
Autologous			
Durham *et al.*[2]	18–27	5–50	?
Dresdale *et al.*[3]	21 6	500–1000	?

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(*Figure 1*). The following were calculated: stress (F/A – g/mm^2), strain (e/ℓ – mm/mm), energy absorption (WD/vol – gmm/mm^2) and elastic modulus (stress/strain – g/mm^2). The mean and standard error of the mean(s.e.m.) were calculated for each glue formulation. As the data were not normally distributed, statistical comparisons were performed using the Mann–Whitney U-test

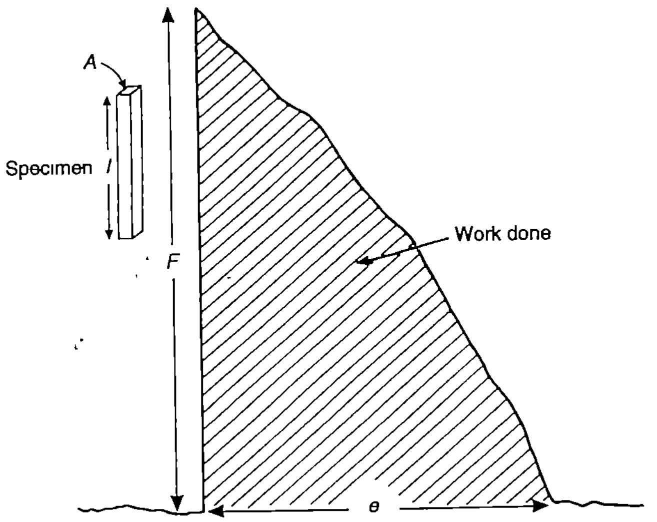

Figure 1 *Idealized load–extension curve with diagrammatic representation of a skin strip for mechanical testing. l, Gauge length, F, force necessary to rupture wound; e, amount of stretching before rupture; A, cross-sectional area*

Representative wound specimens from each of the glue formulation categories were sectioned for histological examination, stained for fibrin and examined microscopically.

Results

Variation in the fibrinogen concentration of the glue within the range 23 g/l to 58 g/l altered the mechanical properties of the glued wounds in this rat skin model at 8 days compared with the control wounds (*Table 2*). Wounds treated with a glue with a fibrinogen concentration of 23 g/l did not differ much from control wounds, though they were slightly more elastic. With fibrinogen concentrations of 29 g/l and 39 g/l the wounds were stronger (higher stress and energy values) but more rigid. Wounds closed with a glue with a fibrinogen concentration of 58 g/l showed lower stress and elasticity values than control wounds, though the strain and energy absorption results were not significantly different from those of control wounds.

Mechanical testing of wounds closed with a glue with varying thrombin concentrations showed a similar pattern to the above results (*Table 3*). Wounds treated with a glue with a thrombin concentration of 50 units/ml shows no difference from control wounds. Wounds treated with a glue with a thrombin concentration of 200 units/ml and 600 units/ml resulted in wounds exhibiting significantly higher stress, strain, energy absorption and elasticity values from control wounds. A thrombin concentration of 1000 units/ml in the glue resulted in significantly more elastic wounds with lower stress values.

Alterations in the factor XIII/fibrinogen ratio of the glue between 0·16 and 0·24 did not alter the mechanical properties of glued wounds when compared with control wounds (*Table 4*). Additional varying concentrations of exogenous

Table 2 *Results of mechanical testing when the fibrinogen concentration of the glue is varied keeping the thrombin (200 units/ml), aprotinin (3000 KIu/ml) and calcium (40 μmol/ml) levels constant*

Fibrinogen concentration	Stress	Strain	Energy absorption	Elastic modulus
Control ($n=53$)	35·09(1·94)	0·56(0·03)	6·76(0·42)	66·55(4·02)
58 g/l ($n=47$)	26·77(1·55)*	0·58(0·02)	5·41(0·35)	46·55(2·23)**
39 g/l ($n=36$)	46·91(3·45)**	0·62(0·02)*	11·92(0·70)**	88·69(6·04)**
29 g/l ($n=35$)	45·01(1·93)**	0·56(0·02)	9·17(0·39)**	84·38(4·56)*
23 g/l($n=31$)	30·86(1·63)	0·56(0·02)	5·87(0·32)	56·29(3·16)*

Values are mean(s.e.m.). * $P<0·05$; ** $P<0·01$, difference from control; Mann–Whitney U test

Table 3 *Results of mechanical testing when the thrombin concentration of the glue is varied keeping the fibrinogen (39 g/l), aprotinin (3000 KIu/ml) and calcium (40 μmol/ml) levels constant*

Thrombin concentration	Stress	Strain	Energy absorption	Elastic modulus
Control ($n=30$)	30·09(1·64)	0·46(0·02)	4·48(0·53)	65·00(3·56)
50 Units/ml ($n=36$)	33·27(3·11)	0·50(0·02)	5·41(0·70)	66·18(4·62)
200 Units/ml ($n=38$)	41·72(3·35)**	0·55(0·02)*	7·42(0·67)*	75·88(3·87)**
600 Units/ml ($n=31$)	41·50(2·05)**	0·59(0·03)*	7·90(0·77)**	70·49(4·32)*
1000 Units/ml ($n=34$)	25·42(1·98)*	0·47(0·02)	3·98(0·55)	54·38(2·25)*

Values are mean(s.e.m.). * $P<0·05$; ** $P<0·01$, difference from control; Mann–Whitney U test

Table 4 *Results of mechanical testing when the factor XIII/fibrinogen ratio is varied keeping the thrombin (200 units/ml), aprotinin (3000 KIu/ml) and calcium (40 μmol/ml) levels constant*

Factor XIII/fibrinogen	Stress	Strain	Energy absorption	Elastic modulus
Control ($n=32$)	38·67(2·17)	0·43(0·04)	5·37(0·52)	94·32(4·89)
0·237 ($n=32$)	44·99(3·28)	0·55(0·03)	7·98(0·68)	85·02(6·04)
0·218 ($n=33$)	40·93(1·97)	0·48(0·03)	6·07(0·77)	88·86(5·84)
0·199 ($n=33$)	39·61(1·82)	0·48(0·05)	6·13(0·62)	86·31(3·62)
0·180 ($n=31$)	50·91(3·75)	0·51(0·02)	8·17(0·98)	101·18(7·38)
0·161 ($n=32$)	41·33(2·28)	0·44(0·04)	5·76(0·53)	93·78(3·94)

Values are mean(s.e.m.)

Table 5 *Results of mechanical testing when varying concentrations of factor XIII (FXIII) were added to a glue with fixed concentrations of fibrinogen, thrombin (200 units/ml), aprotinin (3000 KIu/ml) and calcium (40 µmol/ml)*

Concentration of added FXIII [FXIII/Fibrinogen ratio]	Stress	Strain	Energy absorption	Elastic modulus
Control [0·142] ($n=72$)	69·93(3·03)	0·57(0·02)	9·20(0·71)	129·23(6·26)
1·0 Units/ml [0·187] ($n=62$)	69·42(5·58)	0·46(0·02)**	8·53(0·96)	155·37(11·1)
6·0 Units/ml [0·382] ($n=50$)	65·15(4·18)	0·54(0·02)	8·93(0·55)	118·32(6·08)
12·5 Units/ml [0·642] ($n=84$)	66·15(2·91)	0·54(0·01)	9·05(0·49)	123·48(5·24)

Values are mean(s.e.m.) ** $P<0·01$, difference from control; Mann–Whitney *U* test

factor XIII to the glue did not influence the mechanical properties of the glued and control wounds. For the latter two experiments involving factor XIII, a fibrinogen preparation deficient in factor XIII was used.

Microscopy of the wound sections stained for fibrin showed no fibrin in the wounds at 8 days.

Discussion

Tissue adhesives may be used as an adjunct to suturing or stapling attempting to reduce leakage rates, particularly from high-risk anastomoses e g. oesophageal. Cyanoacrylate glues have not been helpful in this area[4,5]. To date, reports on the use of fibrin glue to strengthen sutured intestinal anastomoses have failed to confirm significant benefit over suture/stapling alone[6–10]. A report on 355 patients indicated a lower leak rate of fibrin sealed anastomosis compared with non-glued anastomoses[11]. In this retrospective study, however, all gastrointestinal anastomoses were included (as distinct from high-risk ones) and no details of the anastomotic technique were given (sutured or stapled; one or two layered).

Indifferent results with fibrin glue to date may be due to inappropriate formulation which, in addition to influencing the adhesive properties of the glue, may have detrimental effects on the wound healing process. High concentrations of fibrinogen and thrombin have been shown to inhibit the activity of neutrophils and macrophages[10,12,13]. The problem is compounded by marked variation in the composition of commercially available glues with respect to the concentration of fibrinogen, thrombin and factor XIII levels. Optimal formulation of a fibrin-based glue resulting in good adhesive/sealant properties without adverse effect on the wound healing process was needed. Further experimental and clinical evaluation of this preparation in difficult gastrointestinal anastomoses would then be possible.

The data from this study indicate that inhibition of wound healing was observed at a fibrinogen concentration of 58 g/l and a thrombin concentration of 1000 units/ml. Fibrinogen concentrations of 29–39 g/l and thrombin concentrations of 200–600 units/ml significantly increased stress, energy absorption and elasticity values of the wounds. These parameters reflect improved wound healing rather than enhanced adhesiveness of the glue, as by 8 days all traces of the glue had disappeared. *Table 1* shows that commercially available glues contain considerably more than 39 g/l of fibrinogen on reconstitution. The Lille product showed greater tensile strength at such a high fibrinogen concentration[14] but the test used[15] measured only the strength of the glue and not the ultimate wound strength. This data suggests that the presently available commercial glues may not have an optimum fibrinogen concentration to enable satisfactory wound healing.

In the two experiments looking specifically at factor XIII a fibrinogen preparation deficient in factor XIII was used. The lack of native factor XIII in these formulations may account for the lack of difference between the mechanical properties of the glued and control wounds, despite what would seem adequate levels of fibrinogen and thrombin. From these results it seems that the addition of extra exogenous factor XIII to the glue formulation is not necessary. The native factor XIII which is loosely bound to fibrinogen through the various manufacturing processes is adequate for the efficacy of the glue.

The data from the present study have provided the necessary information for the optimal formulation of fibrin glues based on measured biological effects on wound healing. Evaluation of this formulation in experimental models of high risk intestinal anastomoses is now required.

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Node negative breast cancer: the prognostic value of DNA ploidy for long-term survival

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The DNA content of breast tumours from 170 patients who presented between 1978 and 1980 was measured by flow cytometry. The relationship between tumour ploidy and disease outcome was assessed and its association with other prognostic factors evaluated. Compared with those with diploid tumours, patients with aneuploid tumours had significantly earlier relapse and shorter survival ($P<0{\cdot}0001$)*. Tumour ploidy was strongly related to grade* ($P<0{\cdot}001$)*, but there was no significant association between DNA ploidy and c-*erb*-B-2 expression, lymph node status or tumour size. In lymph node negative and c-*erb*-B-2 negative patients, aneuploid tumours were associated with a poorer prognosis* ($P<0{\cdot}001$) *than diploid tumours. Multivariate analysis showed that tumour ploidy gave independent information on disease free and overall survival. Tumour ploidy may be used as an independent prognostic variable in patients with breast cancer and it may be helpful in defining patients within the node negative or c-*erb*-B-2 negative groups likely to have a poor outcome who might benefit from adjuvant treatment.*

The number of axillary lymph nodes involved by tumour metastasis is the single most important prognostic factor for women with primary breast cancer[1]. The proportion of patients with node negative breast cancer will probably increase with the implementation of screening programmes, and considerable controversy exists regarding their management. Most have a good prognosis, with 75 per cent surviving 10 years, and the majority are not routinely given adjuvant systemic treatment after primary surgery[2]. The National Cancer Institute has suggested that all patients with breast cancer, regardless of axillary node status or other risk factors, should now be considered for adjuvant treatment[3]. Recent studies have indicated that patients with breast cancer with tumours failing to express the oncoprotein c-*erb*-B-2 have a good outcome and may form another good prognostic group[4]. Should these patients be considered candidates for adjuvant therapy? Since only a minority of node negative patients may benefit from adjuvant therapy, the question of which patients in this good prognostic group should be selected for adjuvant treatment (which can carry a significant morbidity and mortality rate) needs to be addressed.

The nuclear DNA content of tumours determined by flow cytometry has emerged as an important prognostic factor in breast cancer. Previous publications have demonstrated an association between DNA content and prognosis, remission time, disease free survival, lymph node involvement, histological grade and oncoprotein expression, but the results are not uniform[5–8]. The prognostic value of DNA content analysis is still unsettled[9,10], and few reports have focused exclusively on patients in good prognostic groups and with long-term follow-up.

The aim of this study was to use flow cytometry to measure DNA ploidy in breast tumours from patients with a minimum of 10 years follow-up and to relate ploidy to other prognostic factors. The relevance of DNA ploidy in the selection of patients from within groups who have a generally favourable outcome, who may benefit from adjuvant therapy, was to be defined.

Patients and methods

Patients

Two hundred patients presenting with stage I and II primary breast cancer at the Royal Victoria Infirmary, Newcastle upon Tyne between 1978 and 1980 were studied. Full clinical details were obtained, with a minimum of 10 years follow-up Surgery consisted principally of simple mastectomy with axillary node sampling Of these 200 patients, paraffin blocks for DNA content determination were available in 196 cases. None of the patients received radiotherapy before surgery.

*Histological grade and c-*erb*-B-2 expression*

Histological grading of the tumours was performed by an experienced histologist (J.A.H.) without prior knowledge of DNA ploidy and follow-up. Tumours were classified according to Elston's modification of the Bloom and Richardson grading[11], grade 1 being well differentiated, grade 2 moderately differentiated and grade 3 poorly differentiated. Immunohistochemical staining for the c-*erb*-B-2 oncoprotein was carried out by an indirect immunoperoxidase technique using the novel monoclonal antibody NCL-CB11 (Novocastra Laboratories, Newcastle upon Tyne, UK)[12]. Tumours were scored according to intensity of membrane staining as either c-*erb*-B-2 negative or positive.

DNA flow cytometry

Paraffin-embedded tumour tissues were processed for DNA flow cytometry after the method of Hedley *et al.*[13,21]. Briefly, 40 μm sections were cut for DNA analysis and one or more adjacent 5 μm control sections were cut for evaluation of c-*erb*-B-2 expression and histological grade. Sections were dewaxed, rehydrated through a series of ethanol solutions into water, and treated with 1 per cent pepsin pH 2 (Sigma P7012, Poole, UK). After filtration through a 35 μm nylon mesh, the nuclei were treated with 0 5 mg/ml RNAase (Sigma R-5503) and stained with 50 μg/ml RNAase (Sigma R-5503) and with 50 μg/ml propidium iodide (Fluka 81845, Glossop, UK)

The DNA analysis was performed on a Becton Dickinson FACS 420 flow cytometer (Cowley, Oxford, UK) The 488 nm line of an argon laser run at 400 mW was used for fluorescence excitation A 585 ± 42 nm bandpass filter and a linear amplifier were used to detect propidium iodide fluorescence. Ten thousand events for each sample were stored and analysed with Consort 30 software (Becton Dickinson Immunocytometry Systems 1988) Fresh human lymphocytes and fixed benign breast tissue sections were used as controls to standardize the fluorescence intensity scale. As the staining intensity of fixed nuclei varied from one sample to another, no external standard was included. The peak with lowest fluorescence intensity in the DNA histogram was regarded as representing the diploid cells. In most of the samples, fibroblasts, lymphocytes and normal epithelial cells were included in this peak and could be regarded as an internal standard Samples were classified as aneuploid if they contained more than one peak. (Any second peak at or near the tetraploid position was considered to indicate aneuploidy only if it contained more than 10 per cent of the total

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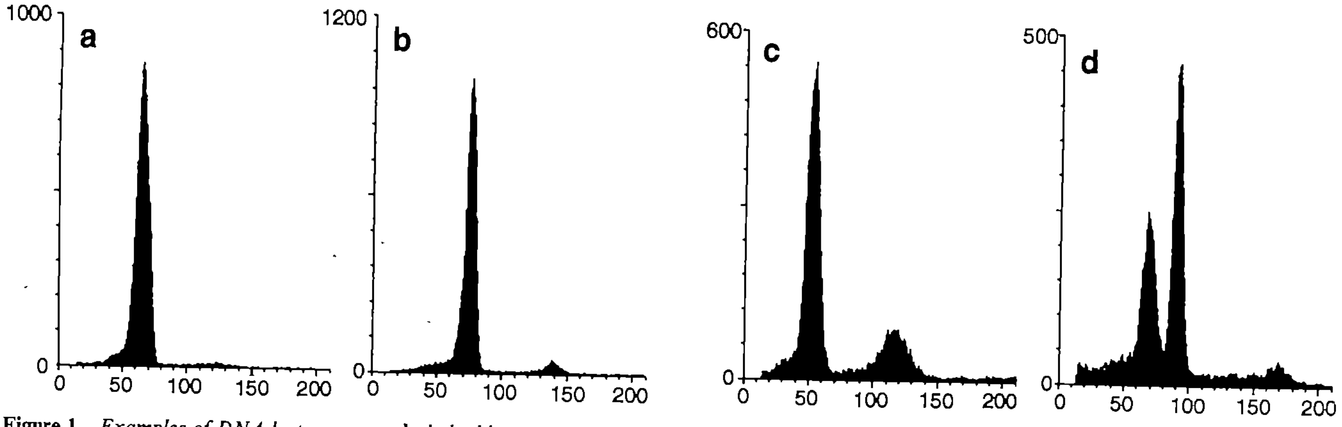

Figure 1 *Examples of DNA histograms* **a**, **b** *diploid histograms (less than 10 per cent of nuclei in the tetraploid position),* **c**, **d** *histograms considered aneuploid (***c** *having greater than 10 per cent of nuclei in the tetraploid position and* **d** *having the second peak outside the tetraploid position)*

number of nuclei) All other samples were classified as diploid (*Figure 1*). DNA histograms were analysed without any information on patient clinical variables and follow-up. In this study, samples were excluded if the coefficient of variation (CV) of the diploid peak was >10.

Statistical analysis

Possible correlations between the results of DNA analysis and menopausal status, tumour size, histological grade, nodal status and c-*erb*-B-2 expression were examined using the χ^2 test, with Yates' correction. Univariate analysis, by the log-rank test, was used to assess the influence of ploidy on disease free and overall survival, and a multivariate analysis using the Cox regression model was performed.

Results

The CV of the diploid peak ranged from 4·5 to 14·2 (mean 6·7) and resulted in the exclusion of 12 tumours having a diploid peak with a CV >10. A further six tumours with an uninterpretable DNA histogram and eight sections from patients who had received chemotherapy after surgery were also excluded. Therefore, 170 of 196 (87 per cent) of the paraffin blocks were used for DNA histogram analysis, and details of the clinical variables relating to these patients are listed in *Table 1*. Sixty-one (36 per cent) of the 170 tumours were found to be diploid and 109 (64 per cent) aneuploid. The relationship between tumour ploidy and the clinical characteristics is shown in *Table 2* The DNA ploidy was not significantly related to menopausal status ($P=0{\cdot}3$), tumour size ($P=0{\cdot}1$), nodal status ($P=0{\cdot}08$) or c-*erb*-B-2 expression ($P=0{\cdot}09$), but was significantly related to histological grade ($P<0{\cdot}001$) Compared with diploid tumours, patients with aneuploid tumours had significantly earlier relapse and shorter overall survival times. Seventy-two per cent of patients with aneuploid tumours and 39 per cent of those with diploid tumours had relapsed ($P<0{\cdot}0001$), and 66 per cent of patients with aneuploid tumours and 33 per cent with diploid tumours had died from breast cancer at 10 years ($P<0{\cdot}0001$) (*Figure 2*). In patients with node negative disease ($n=120$), 65 per cent of those with aneuploid tumours and 27 per cent with diploid tumours had relapsed ($P<0{\cdot}0001$), and 62 per cent of patients with aneuploid tumours, compared with 18 per cent with diploid tumours, had died ($P<0{\cdot}0001$) (*Figure 3*). In patients with c-*erb*-B-2 negative expression ($n=122$), 75 per cent of those with aneuploid tumours and 37 per cent with diploid tumours had relapsed ($P<0{\cdot}0001$), and 62 per cent of patients with aneuploid tumours, but only 35 per cent with diploid tumours had died ($P=0{\cdot}00295$) (*Figure 4*).

Table 1 *Patient characteristics*

No of patients	170
Age (years)	
Median	56
Range	33–88
Axillary nodes	
Negative	120 (71)
Positive	50 (29)
Menopausal status	
Premenopausal	48 (28)
Postmenopausal	123 (72)
Histological grade	
Grade 1	15 (10)
Grade 2	61 (40)
Grade 3	75 (50)
Unknown	19
c-*erb*-B-2 expression	
Negative	122 (77)
Positive	36 (23)
Unknown	12
Tumour size	
T_1 (≤2 cm)	70 (43)
T_2 (>2 cm)	91 (57)
Unknown	9

Values in parentheses are percentages

Table 2 *Relationship between DNA ploidy and variables*

Variables	Aneuploid (n)	Diploid (n)	P value*
Menopausal status			
Premenopausal	28	20	
Postmenopausal	81	41	0·3
Bloom and Richardson grade			
1	3	12	
2	34	27	
3	61	14	<0·001
Nodal status			
Positive	37	13	
Negative	72	48	0·08
c-*erb*-B-2			
Positive	28	8	
Negative	76	46	0·09
Tumour size			
T_1	39	31	
T_2	62	29	0·1

* χ^2 test with Yates' correction

Menopausal status, histological grade, axillary node status, tumour size, c-*erb*-B-2 expression and DNA ploidy were analysed as factors for disease free survival (DFS) and overall survival (OS) (*Table 3*). All except menopausal status were of significant prognostic value for both DFS and OS on univariate analysis. The most important independent prognostic factor in multivariate analysis was axillary node status (DFS, $P<0{\cdot}001$, OS, $P<0{\cdot}02$), followed by DNA ploidy (DFS, $P<0{\cdot}02$, OS, $P<0{\cdot}05$) and c-*erb*-B-2 expression (OS, $P<0{\cdot}05$, DFS, n s.). Histological grade, tumour size and menopausal status did not show independent prognostic value (*Table 3*) In patients with negative axillary nodes ($n=120$), the results of multivariate

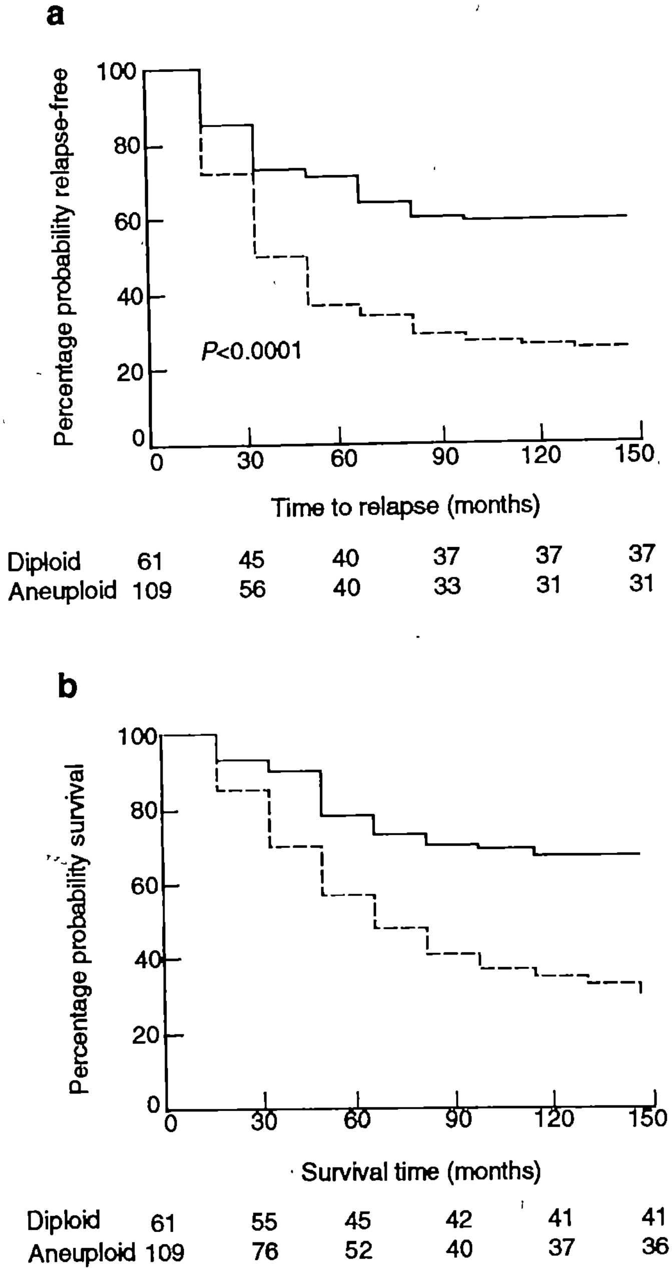

Figure 2 *Ploidy related to disease free and overall survival:* **a** *relationship of tumour ploidy to the probability of relapse* versus *time for all patients:* **b** *probability of survival.* ——, *Diploid,* – – –, *aneuploid*

analysis still demonstrated that DNA ploidy (DFS and OS, $P<0{\cdot}01$) and c-*erb*-B-2 expression (DFS, n.s.; OS, $P<0{\cdot}05$) were independent prognostic indicators. In patients negative for c-*erb*-B-2 expression ($n=122$), axillary node status (DFS, $P<0{\cdot}001$; OS, $P<0{\cdot}01$) showed independent prognostic value, but DNA ploidy was only of independent prognostic value for disease free survival ($P<0{\cdot}02$).

It was noted that, if the cut-off point for the size of the peak at or near the tetraploid position was increased from 10 to 15 per cent, 11 tumours were reclassified from aneuploid to diploid, resulting in a reduction of the percentage of aneuploid tumours from 64 to 58 per cent. With this classification, 73 per cent of the patients with aneuploid tumours had relapsed and 66 per cent had died, and 49 per cent of those with diploid tumours had relapsed and 43 per cent had died (DFS, $P=0{\cdot}00429$; OS, $P=0{\cdot}00991$). In Cox's analysis, ploidy no longer showed as an independent prognostic variable (DFS and OS, $P>0{\cdot}1$).

Discussion

The proportion of aneuploid tumours in this study (64 per cent) is close to that reported by others[6,7,14–18], but levels of aneuploid tumour distribution as high as 89 per cent have been observed[19]. Such differences in DNA distribution may be caused by selection of patients, different fixation procedures or variations in flow cytometric methodology. DNA histograms are not always interpreted in an identical fashion and may result in a different aneuploid percentage being derived by different scientists from the same data set[20]. In the present study, tetraploid peaks were ignored if they contained less than 10 per cent of the total nuclei. If the cut-off point was increased from 10 to 15 per cent, as others have done[10,15], aneuploid tumours were still associated with a poorer prognosis than diploid tumours. DNA ploidy was no longer of independent prognostic value. Some authors have used 5 per cent as cut-off point[20].

The variable most strongly associated with DNA ploidy in the study was histological grade, which in itself was a good predictor of clinical outcome on univariate analysis. Aneuploidy was strongly associated with poorly differentiated tumours, which is in agreement with other studies[7,14,15,18,19,22]. As in

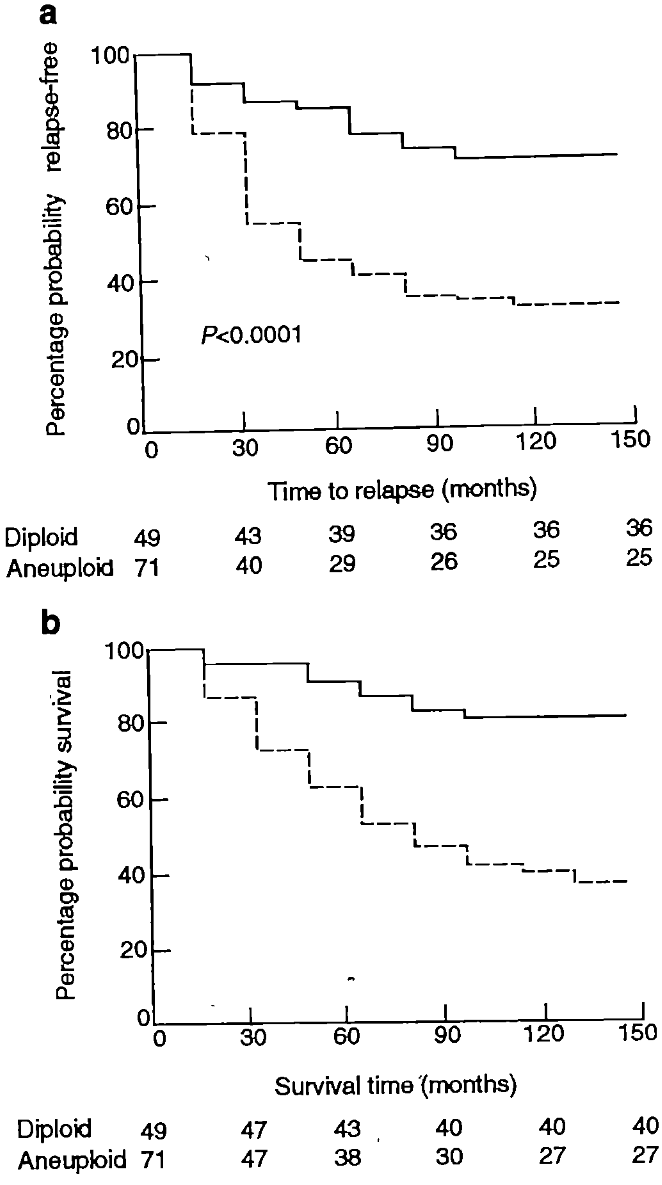

Figure 3 *Node negative patients stratified by tumour ploidy:* **a** *probability of relapse free survival,* **b** *overall survival* ——, *Diploid;* – – –, *aneuploid*

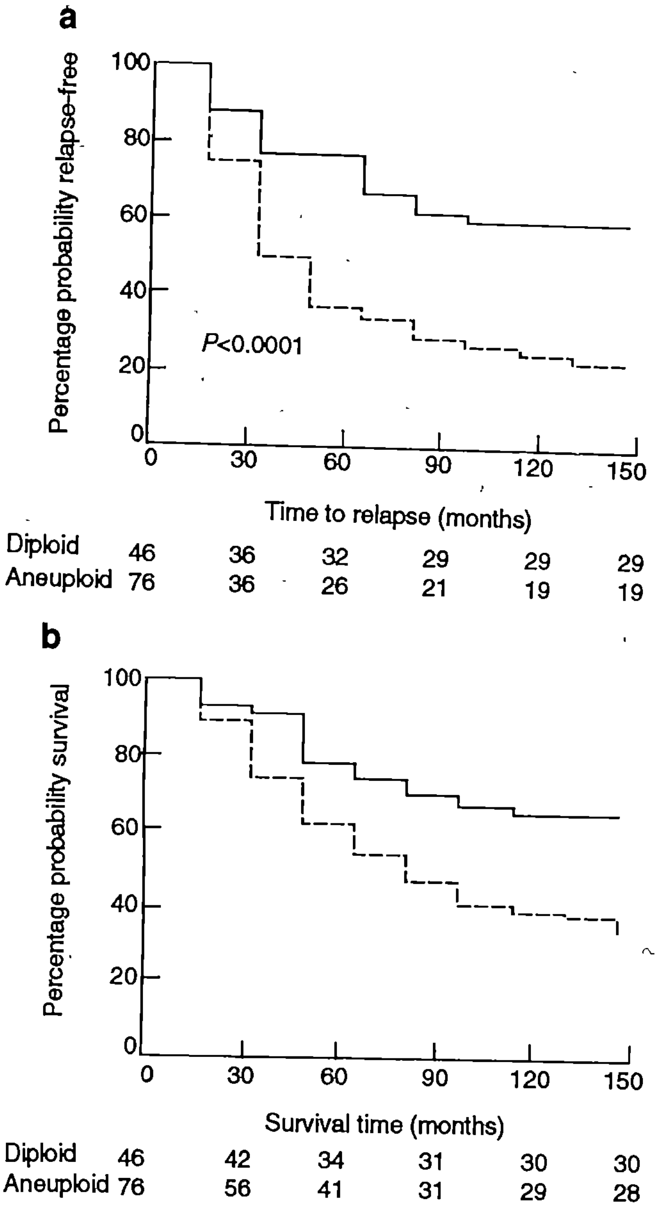

Figure 4 *c-*erb*-B-2 negative patients stratified by tumour ploidy: **a** relapse free survival, **b** overall survival.* ——, *Diploid,* ---, *aneuploid*

Table 3 *Results of univariate and multivariate analysis*

	P value			
	Univariate†		Multivariate‡	
Variables	DFS	OS	DFS	OS
Node status	<0·001*	<0·001*	<0·001*	<0·02*
DNA ploidy	<0·005*	<0·01*	<0·02*	<0·05*
Bloom and Richardson grade	<0·005*	<0·001*	0·6	0·2
c-*erb*-B-2 expression	<0·02*	<0·007*	0·1	<0·05*
Menopausal status	0·3	0·4	0·8	0·6
Tumour size	<0·001*	<0·001*	0·6	0·2

DFS, disease free survival; OS, overall survival. * Statistically significant, † log-rank test, ‡ Cox regression model

other reports, a statistically significant relationship between DNA ploidy and nodal status, tumour size, menopausal status and c-*erb*-B-2 expression was not demonstrated[7,15,18]. Some reports have indicated that aneuploidy was significantly related to node positive tumours[14,17].

The outcome for patients in this study was significantly related to tumour ploidy. Patients with aneuploid tumours had shorter disease free and overall survival, with more than half of these patients relapsing within the first 3 years and almost half dying within the first 5 years after primary surgery. Previous studies have reported similar results[5,6,14,17] but have failed to show significant differences in survival between diploid and aneuploid tumours[15,18]. The difference in disease outcome between patients with diploid and aneuploid tumours is also seen for node negative and c-*erb*-B-2 negative groups, with aneuploidy being significantly adversely related to both relapse and survival.

Most authors agree that abnormal DNA ploidy is associated with unfavourable survival in patients with breast cancer. In the majority of studies this association has, however, been weak, and it has been significant only on univariate analysis To examine the relative importance of DNA ploidy as a prognostic factor in breast cancer, the independent prognostic significance of these results must be assessed by multivariate analysis Axillary node status was the most important independent prognostic indicator of disease free and overall survival, followed by DNA ploidy and c-*erb*-B-2 expression. Tumour grade, tumour size and menopausal status were not significant independent variables when related to prognosis. These findings confirmed the results of Kallioniemi *et al.*[14], given some minor methodological differences between the two studies.

With the advent of the National Breast Screening Programme the number of women presenting with node negative breast cancer will increase. Accumulating evidence indicates that abnormalities in oncogene expression such as c-*erb*-B-2[23] and NM 34[24] are are common in breast cancer and may be indicators of poor prognosis, but few studies have focused on the relationship between c-*erb*-B-2 expression and DNA ploidy. Identification of women with potentially poor outcome from within good prognostic groups is difficult and tumour ploidy may have an important role.

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Autopsy-verified pulmonary embolism in a surgical department: analysis of the period from 1951 to 1988

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A retrospective analysis was undertaken of all surgical patients in Malmö, Sweden, during the period from 1951 to 1988 in whom pulmonary emboli were found at autopsy. The analysis included a comparison with the earlier analysed and reported time period from 1951 to 1980. A continued high frequency of pulmonary embolism at autopsy was seen during the 1980s (20·3 per cent of deaths, 31·7 per cent of autopsies). Of the 391 autopsy-verified pulmonary emboli found between 1981 and 1988, 113 (28·9 per cent) were considered fatal, 104 (26·6 per cent) contributed to death and 174 (44·5 per cent) were incidental. Few patients had symptomatic deep vein thrombosis or pulmonary embolism before death. The overall frequency of major pulmonary embolism in surgical patients remained unchanged (0·3 per cent). The frequency of major postoperative pulmonary embolism showed an increase during the 1950s and 1960s (maximum 0·4 per cent) but a decrease in the last 5-year period of the 1970s (0·3 per cent), which has earlier been reported upon. This decrease continued during the 1980s (0·2 per cent) ($P<0{\cdot}05$). An increase was found in the number of patients operated on who had autopsy-proven pulmonary embolism and who received thromboprophylaxis. Pulmonary embolism continues to be a major cause of death in surgical patients; however, postoperative major pulmonary embolism has shown a reduction in the last 15-year period.

Postoperative fatal pulmonary embolism is considered an avoidable cause of death. Proper prophylactic measures can prevent or at least make it less frequent[1–3]. We have previously reported on changes in the pattern of pulmonary embolism in surgical patients, whether operated on or not, during the 30-year period from 1951 to 1980[4]. The data revealed an increase in pulmonary embolism during the 1950s and 1960s, and a slight but significant reduction in the last 5-year period of the 1970s. This continued survey of the 1980s was undertaken with the aim of analysing whether progress in medical care, with better diagnostic tools, new pharmacological treatments, more frequent use of thromboembolism prophylaxis and advances in anaesthesia and intensive care, has further contributed to a reduction in the frequency of thromboembolism in surgical patients.

All autopsies from the surgical department at Malmö General Hospital during the time period from 1951 to 1988 were scrutinized. A comparison is made with data from the previously analysed and reported time period from 1951 to 1980[4].

Patients and methods

The city of Malmö (230 000 inhabitants) is served by one hospital to which all patients needing hospitalization are referred. All autopsy reports from the department of surgery during the period from 1951 to 1988 were reviewed and all cases of pulmonary embolism were further analysed. During this period routine post-mortem examination was performed with dissection of the pulmonary arterial tree to at least segmental level and with exposure of the vessels of the leg to the mid-thigh region to detect thrombus. A microscopic lung examination was always included.

Based on data from autopsy reports and patient records the pulmonary emboli were classified as follows.

1. Fatal pulmonary emboli. No other cause of death found at autopsy. Emboli occluding at least two lobar arteries
2. Contributory pulmonary emboli. In addition to pulmonary embolism, other pathological factors were involved in causing death. Emboli occluding at least one lobar or multiple segmental artery.
3. Incidental pulmonary emboli. Small or old pulmonary emboli considered to have had no influence on the fatal outcome

Postoperative pulmonary embolism was defined as occurring within 30 days of operation. Life expectancy of 5 years was considered to exist if surgery was for benign disease or was radical and curative for malignancy, combined with a patient age 5 years less than the mean survival age for females (79 years) or males (74 years)

The number of patients and autopsies is shown in *Table 1*. For statistical analysis data were divided into 5-year periods, except for 1986–88. Statistical calculations were made with the χ^2 test

Results

From a total of 1925 deaths during 1981–88, 1234 autopsies (64·1 per cent) were performed (*Table 1*). Death within 30 days of surgery occurred in 811 patients of whom 187 (23·1 per cent) did not undergo autopsy. Autopsy-verified pulmonary embolism was noted in 391 cases (20·3 per cent of deaths, 31·7 per cent of autopsies). In *Table 2* the classification of emboli is shown as well as the numbers of autopsies revealing pulmonary embolism during the time period from 1951 to 1988. The incidence of autopsy-verified pulmonary embolism increased during the 1950s and 1960s, after which a decline occurred. *Figure 1* relates the number of fatal and contributory pulmonary emboli (major pulmonary emboli) to the number of hospitalized patients and to the number of patients operated on. The increase during the 1950s and 1960s was followed by a decrease during the 1970s. During the 1980s no further reduction in the total number of major pulmonary embolism

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Table 1 *Numbers of patients, operations, deaths and autopsies*

Time period	No. of hospitalized patients	No. of patients operated on	No. of deaths	No. of autopsies	Autopsy frequency (%)
1951–55	25 864	17 472	620	618	99·7
1956–60	30 352	19 149	551	547	99·3
1961–65	31 876	18 832	687	685	99 7
1966–70	34 197	19 522	990	916	92·5
1971–75	42 373	23 585	1320	1206	91 4
1976–80	43 390	20 969	1309	1079	82·4
1981–85	45 848	18 896	1134	736	64·9
1986–88	26 690	12 342	791	498	63 0

Table 2 *Numbers of patients with autopsy-verified pulmonary embolism from 1951 to 1988*

	No with fatal pulmonary embolism		No. with contributory pulmonary embolism		No with incidental pulmonary embolism	
Time period	Total hospitalized patients	Patients operated on	Total hospitalized patients	Patients operated on	Total hospitalized patients	Patients operated on
1951–55	43	29	6	2	0	0
1956–60	52	30	19	13	15	9
1961–65	49	31	60	40	88	45
1966–70	76	40	76	43	131	63
1971–75	77	37	107	54	168	73
1976–80	52	28	85	38	170	81
1981–85	70	17	64	18	114	46
1986–88	43 (72)	13 (22)	40 (67)	9 (15)	60 (100)	21 (35)

Values in parentheses are corrected figures for a 5-year period

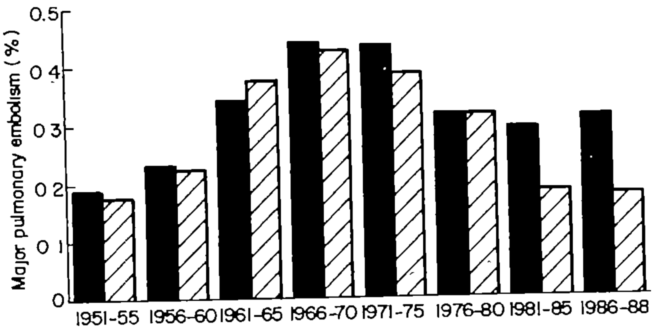

Figure 1 *Frequency of major pulmonary embolism (fatal and contributory) in total hospitalized patients* (■) *and patients operated on* (▨)

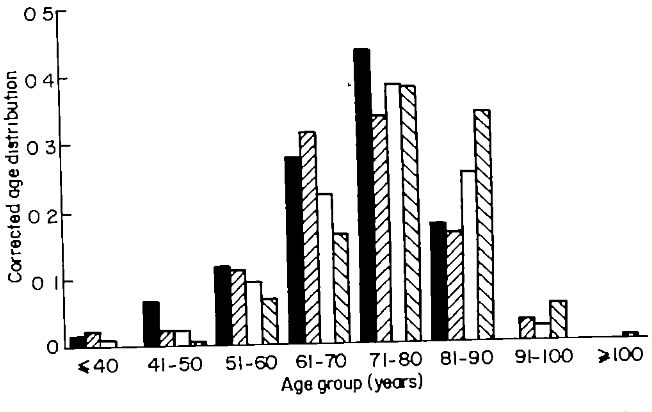

Figure 2 *Corrected age distribution for all surgical patients (whether operated on or not) with fatal or contributory pulmonary embolism between 1951 and 1988, grouped into 10-year periods.* ■, *1951–60;* ▨, *1961–70;* □, *1971–80;* ▧, *1981–88*

occurred, but postoperative major embolism was further reduced ($P < 0.05$) In patients not undergoing operation the incidence of major pulmonary embolism at autopsy was 26·2 per cent (160 major pulmonary emboli at 610 autopsies) compared with 9·1 per cent (57 major pulmonary emboli at 624 autopsies) in patients who had undergone surgery within 30 days of death.

The age distribution of patients with fatal and contributory pulmonary embolism changed with time; older patients were more affected in later decades The median age was 77 years in 1981–88 compared with 68 years in 1951–60 ($P < 0.01$). The change in age distribution is shown in *Figure 2* for the total population and in *Figure 3* for postoperative patients. The proportion of women increased from 36 per cent during the 1950s, to 50 per cent during the 1960s, 57 per cent during the 1970s and 59 per cent during the last decade. Patients with fatal and contributory emboli had malignancy in 70 per cent of instances in the last decade. Lung infarction was seen in 42 (37 per cent) of 113 cases with fatal pulmonary embolism, and in 47 (45 per cent) of 104 patients with contributory pulmonary embolism. Fewer patients with fatal postoperative pulmonary embolism were seen the last decade who were operated on for a benign disease or for a curable malignancy: 56 per cent compared with 76 per cent for the time period from 1951 to 1980 ($P < 0.05$). No change was seen for patients with contributory (52 *versus* 48 per cent) or incidental embolism (54 *versus* 59 per cent). An expected survival time of at least 5 years if pulmonary embolism had not occurred was regarded as present in only 31 per cent of patients operated on with fatal or contributory pulmonary embolism in the last decade.

The types of operation performed during the last decade and during the earlier time period are shown in *Table 3*. The frequency of use of thrombosis prophylaxis among patients with autopsy-verified major pulmonary embolism increased from 50 per cent in 1971–75, to 76 per cent in 1976–80, 85 per cent in 1979–83 and 94 per cent in 1984–88. The median hospitalization time after operation during the last decade was 16 days (range 1–30 days) for patients with fatal, and 15 days (range 1–30 days) for patients with contributory postoperative pulmonary emboli. In *Figure 4* the time interval between operation and death in patients with fatal or contributory postoperative pulmonary emboli is shown for the last two decades.

At routine autopsy calf veins were not examined. Location of the detected thrombi is given in *Table 4*. In the last decade, 19 patients had subclavian or axillary vein thrombosis, with superior vena cava involvement in five cases. These thrombi were caused by indwelling central venous lines in all except one patient who had a lung malignancy.

Discussion

An overall analysis of pulmonary embolism among all surgical patients over a period of 38 years reveals an overall unaltered frequency in the last 15-year period. There are, however, several factors that favour an increased risk of pulmonary embolism over the years: older age distribution, the fact that fewer patients with terminal stage disease are taken care of at home, and more and older patients undergoing extensive cancer operations and reconstructive procedures (e.g. vascular). In spite of this a reduction, without correction for risk factor change, was seen in the frequency of postoperative fatal and contributory pulmonary emboli in the last 15-year period. This started between 1976 and 1980 (during our previous survey of the time period from 1951 to 1980) and continued in an even more marked fashion between 1981 and 1988. This finding is in accordance with the reports from Edinburgh[5] and Duluth, Minnesota[6].

A major drawback of this analysis of pulmonary embolism is the change in autopsy frequency, which must be taken into consideration when analysing the present data The earlier impressive autopsy rate was reduced by a change in legislation in 1978 and by economic factors. However, cases with an uncertain cause of death and postoperative deaths in general have been given the highest priority for post-mortem examination. During the 1980s 624 of the 811 patients who died within 30 days of surgery underwent autopsy. The records of those who did not undergo autopsy have been analysed and in only three cases was there clinical suspicion of pulmonary embolism. However, clinical evaluation of terminal disease and thromboembolism is unreliable and has been regarded as soft data, and is not included in the present results. The autopsy rate during the 1980s is still high in comparison with other reports, but the change in frequency may influence the validity of our overall results.

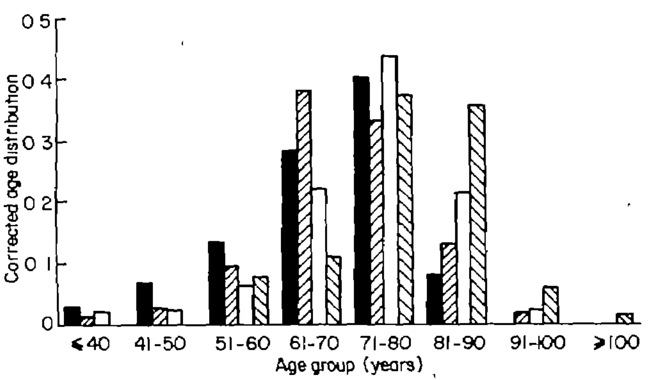

Figure 3 *Corrected age distribution for surgical patients operated on with postoperative fatal or contributory pulmonary embolism between 1951 and 1988, grouped into 10-year periods.* ■, *1951–60;* ■, *1961–70,* □, *1971–80;* ■, *1981–88*

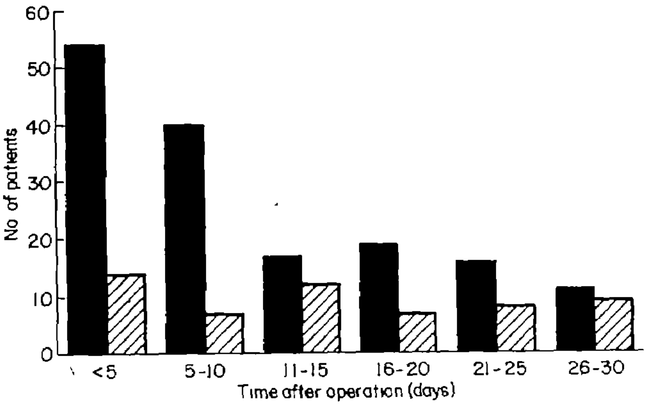

Figure 4 *Time interval between operation and death in patients with postoperative fatal or contributory pulmonary embolism during 1971–80* (■) *and 1981–88* (■)

Table 3 *Types of operation performed on patients with major postoperative pulmonary embolism between 1951 and 1980, and between 1981 and 1988*

	1951–80		1981–88	
	Fatal	Contributory	Fatal	Contributory
Malignancy, non-radical	47	99	13	9
Malignancy, radical	36	30	4	3
Cholecystectomy	15	6	0	1
Appendicectomy	13	1	0	0
Diverticulitis	7	4	0	0
Intestinal obstruction	10	14	4	2
Incarcerated hernia	10	2	0	0
Emergency stomach surgery	12	14	1	2
Elective stomach surgery	10	7	0	0
Embolectomy	3	2	4	3
Vascular reconstructive surgery	5	4	2	5
Others	27	7	2	2
Total	195	190	30	27

Table 4 *Number of patients with venous thrombi detected at different loci (as a percentage of the number of patients with pulmonary emboli), between 1951 and 1980, and 1981 and 1988*

	1951–80			1981–88		
	Fatal ($n=349$)	Contributory ($n=353$)	Incidental ($n=572$)	Fatal ($n=113$)	Contributory ($n=104$)	Incidental ($n=174$)
No thrombus found	30	28	45	19	35	60
Bilateral iliofemoral DVT	33	38	23	42	38	22
Left iliofemoral DVT	17	17	12	12	14	8
Right iliofemoral DVT	17	11	9	14	12	6
Upper extremity	2	5	3	4	13	2
Others	3	6	11	5	1	7
Inferior vena cava				8	2	7
Portal vein				4	5	3

DVT, deep vein thrombosis

The reduction in frequency of postoperative pulmonary embolism coincides with an increased use of thrombosis prophylaxis The present data support the view that a general usage of thrombosis prophylaxis may reduce serious pulmonary embolism within a total surgical population. Convincing support of the benefit of such prophylaxis is also seen in the extensive literature on prevention of postoperative thromboembolism[1–3]. The frequency of postoperative fatal pulmonary embolism of 0·1 per cent (30 out of 31 238) during the 1980s in our unselected population is of the same order of magnitude as that found in controlled trials of thrombosis prophylaxis[1–3].

The problems with retrospective classification of pulmonary embolism have been discussed previously[4]. That the same senior staff examined all autopsies and that the protocol was not changed during the entire time period increase the validity of the present study. Additionally, when the findings were equivocal, microscopic examination of the thromboembolism was carried out. When evaluating the autopsy reports it was striking how often the thromboembolic event was not suspected during life, but such retrospective data are soft and have therefore not been further analysed. The majority of patients with fatal pulmonary embolism had no clinical symptoms of a deep venous thrombosis or any obvious heralding symptoms It is interesting that in a different population consisting of all patients with phlebographically verified, symptomatic deep venous thrombi at the Malmö General Hospital in 1987, only ten out of 282 patients with thrombosis had clinical signs of pulmonary embolism, verified by perfusion scintigraphy in four[7]. Could it be that the more symptomatic a deep vein thrombus is, the less is the risk of pulmonary embolism? One possibility is that the phlebitic reaction giving rise to local symptoms also anchors the thrombus at the vessel wall.

It is not possible to make any firm conclusion concerning the origin of the pulmonary emboli from this analysis but, as seen in *Table 4*, a large proportion of the patients had no thrombi localized in the thigh region or more proximally at autopsy. Many of these patients could have had popliteal or crural thrombi causing their pulmonary emboli. Thus patients developing silent postoperative popliteal or crural thrombi may be at substantial risk of having a fatal pulmonary embolism. This is in accordance with the findings of a post-mortem study by Havig[8] and with many trials on the prophylactic deployment of the fibrinogen uptake test which may identify silent as well as symptomatic thromboses.

In summary, there has been a continued and maintained reduction during the 1980s of autopsy-verified pulmonary embolism among surgical patients. There has been a continued and further reduction of postoperative major (fatal and contributory) pulmonary embolism.

Acknowledgements

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Fibrinolytic activity of the arms and legs of patients with lower limb venous disease

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Clearance of subcutaneous ^{125}I-labelled fibrin was prolonged from the legs but not from the arms of patients with uncomplicated varicose veins and patients with healed ulcers, compared with controls. The euglobulin clot lysis time (ECLT) of blood from the arms and legs of those with healed ulcers was prolonged; venous congestion significantly shortened the ECLT of blood from all limbs except legs with healed ulcers. The clearance of interstitial fibrin of both legs and arms correlated with the response of the ECLT to venous congestion ($P<0{\cdot}05$)*. The clearance of interstitial ^{125}I-labelled albumin in five patients with healed ulcers was faster from the legs than from the arms, whereas the clearance of interstitial ^{125}I-labelled fibrin was faster from the arms in all cases. These results suggest that there is a defect in interstitial fibrinolytic activity as well as vein wall production of plasminogen activator in legs with chronic venous insufficiency.*

The 'fibrin cuff' hypothesis of Browse and Burnand[1] proposes an important role for diminished interstitial fibrinolytic activity in the development of pericapillary cuffs in lipodermatosclerotic skin and fat, which they suggest block the diffusion of oxygen and nutrients from the blood to the tissues, rendering the skin ischaemic and malnourished and therefore susceptible to ulceration. This paper investigates interstitial fibrinolysis by measuring the rate of lysis of experimentally produced subcutaneous radiolabelled clots of fibrin, and investigates the relationship between plasma fibrinolytic activity, vein wall activator production and interstitial fibrinolysis in normal upper and lower limbs and limbs with chronic venous insufficiency.

Patients and methods

Patients

Normal subjects were recruited from the Department of Surgery. Patients with varicose veins and venous ulcers were recruited from the Department's vascular clinics. The presence of venous insufficiency in patients with clinical venous disease was confirmed by foot volumetry[2]. All patients with healed venous ulcers had normal serological investigations and an ankle–brachial Doppler pressure index >1, thus excluding patients with rheumatoid and ischaemic ulcers. Those taking anticoagulants or fibrinolytic enhancing agents were excluded, as were women of childbearing age and those with normal foot volumetry. None of the patients with simple uncomplicated varicose veins gave a history of deep venous thrombosis or ulceration. The age and sex distributions of these two groups and the control volunteers did not differ significantly.

Formation of radiolabelled clots

Radiolabelled clots were formed by the subcutaneous injection of 0·05 ml (0·2 MBq) ^{125}I-labelled fibrinogen (Amersham International plc, Amersham, UK) followed immediately by 0·05 ml (200 units/ml) human thrombin (Plasma Fractionation Laboratory, Oxford, UK). These two substances were injected 4 mm below the skin surface, into the mid-flexor aspect of the forearm and into the calf, 10 cm above the medial malleolus, through the same fine (21 Fr gauge) needle so that they mixed together at the tip of the needle. Subcutaneous veins, scars of previous ulcers and the subcutaneous border of the tibia were avoided. Radioactivity was measured with a collimated scintillation counter immediately after injection and thereafter every 24 h for 96 h. The radioactivity counts were corrected to take account of the physical half-life of iodine-125. The half-life of the clearance curve was calculated for each injection site by linear regression analysis of a semilogarithmic plot of the corrected activity against time.

Injection of radiolabelled albumin

The clearance of albumin from the limbs of five subjects with healed venous ulceration was measured after the injection of 0·05 ml (0·2 MBq) ^{125}I-labelled human albumin (Amersham International plc). The sites of injection, the measurement of the activity and the calculation of the clearance half-life were as for the fibrin clots. Before injecting the isotopes, subjects were given 5 ml potassium iodide solution (30 mg/ml) orally, and thereafter daily for 3 weeks. Those with a history of iodine sensitivity were excluded.

The euglobulin clot lysis time

After a 1 h recumbent rest, fasting venous blood samples were taken between 8 and 10 a.m. from an antecubital vein and from a dorsal foot vein, without the application of a tourniquet, using a 19 Fr gauge needle and a 10 ml plastic syringe containing 1 ml sodium citrate. Further blood samples were taken after 10 min venous congestion produced by a pneumatic cuff inflated to 80 mmHg pressure. The euglobulin clot lysis time (ECLT) of the separated plasma was measured as the mean of two duplicate samples by the techniques of Blix[3] and Marsh[4]. Non-parametric statistical tests were applied to the data.

Results

Clearance of radiolabelled clots

Both arms and both legs of 33 patients with healed venous ulcers (42 healed lower limbs and 24 lower limbs which had never been ulcerated) and five patients with bilateral varicose veins were studied. One arm and one leg of 11 healthy control subjects were also studied. The injection caused bleeding and localized bruising in one arm of two patients with varicose veins, so these sites were excluded from the study. There were no other local complications and no increase in radioactivity over the thyroid gland in any patient.

There were no significant differences (Mann–Whitney *U* test) between the clearance of fibrin from the arms in the three study groups (*Table 1*). Compared with controls, the clearance of fibrin was prolonged from legs with varicose veins, from non-ulcerated legs of ulcer subjects and from legs with healed ulcers (*Table 1*). The difference between the clearance of fibrin from the arms and legs of the control subjects was not significant (Wilcoxon's test). However, among those in the two other study groups, the clearance of fibrin from legs was prolonged compared with clearance from arms ($P<0{\cdot}01$ for subjects with healed ulcers, $P<0{\cdot}02$ for subjects with varicose veins; Mann–Whitney *U* test).

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Table 1 *Half-life of clearance of fibrin from arms and legs*

	Median (h)	Range (h)	Compared with control limb*
Arms			
Controls	16	11–28	
Subjects with varicose veins	16·5	14–21	n.s
Subjects with healed ulcers	17	11–29	n.s.
Legs			
Controls	15	13–27	
Subjects with varicose veins	23·5	18–37	$P<0{\cdot}05$
Subjects with ulcer			
Non-ulcerated	24·5	15–53	$P<0{\cdot}05$
With healed ulcers	31·5	16–121	$P<0{\cdot}001$

* Mann–Whitney *U* test n s., Not significant

Table 2 *Euglobulin clot lysis time of venous blood samples taken from arms with and without venous congestion*

	Median (min)	Range (min)	Effect of congestion
Controls			
No congestion	157	86–324	$P<0{\cdot}01$
Congestion	69	21–97	
Varicose veins			
No congestion	180	67–307	$P<0{\cdot}05$
Congestion	32	23–86	
Healed ulcers			
No congestion	256*	39–570	$P<0{\cdot}01$
Congestion	99*	30–540	

* Compared with controls, $P<0{\cdot}05$ (Mann–Whitney *U* test)

Clearance of radiolabelled albumin

There were no complications resulting from the measurement of albumin clearance. The median clearance half-life of albumin from the eight legs of the five patients studied with healed ulcers was 15 h (range 11–21 h), and from their ten arms it was 27 h (range 16–39 h). The clearance of albumin from arms was prolonged compared with clearance from legs in all cases (Mann–Whitney *U* test, $P<0{\cdot}001$). By contrast, the median clearance half-life of fibrin from the eight legs of these five patients was 61 h (range 22–121 h), and from their ten arms it was 18 h (range 14–25 h). The clearance of fibrin from legs was prolonged compared with clearance from arms in all cases (Mann–Whitney *U* test; $P<0{\cdot}001$).

Euglobulin clot lysis time

Venous samples were taken with and without venous congestion from all subjects. Samples were taken from the legs of the 11 control subjects, three of the five patients with varicose veins, and 21 of the legs with healed ulcers. Two patients with varicose veins and three patients with healed venous ulcers refused to have samples taken from their legs, and it was impossible to take samples from the legs of nine patients with healed ulcers because of skin thickening and induration, which obscured the superficial veins. Samples were not taken from the non-ulcerated limb of those with healed ulcers.

The median ECLT values for the three groups are shown in *Tables 2* and *3*. The ECLT at rest of venous blood from legs was significantly longer than that of arm vein blood ($P<0{\cdot}05$) in controls and in patients with healed ulcers. The difference between arm and leg resting value for those with varicose veins did not reach statistical significance. Venous congestion shortened the ECLT of venous blood from both the arms and the legs of controls and patients with varicose veins; it also shortened the ECLT of venous blood from the arms but not the legs of patients with healed venous ulcers (*Figures 1* and *2*).

Relation between fibrin clearance half-life and ECLT

Considering all the subjects together, a statistically significant negative correlation was found between fibrin clearance half-life from legs and percentage reduction of ECLT in response to venous congestion (*Figure 3*). This is a weak correlation; the Spearman rank correction coefficient is $-0{\cdot}32$. No correlation was found between fibrin clearance half-life and ECLT at rest or after venous congestion.

Discussion

The best method of measuring tissue or interstitial fibrinolytic activity is by extracting plasminogen activators from a sample of tissue. Tissue biopsy was not applicable to this study because taking skin and subcutaneous tissue biopsies from the gaiter area of the leg, which often had severe lipodermatosclerosis, carries a considerable risk of causing an ulcer. Although it is impossible to be absolutely sure that the injection of ^{125}I-labelled fibrinogen and human thrombin results in the formation of a cross-linked fibrin clot, evidence from a previous pilot study suggests that it does. In rats, thrombin delays the disappearance of subcutaneous ^{125}I-labelled fibrinogen and its omission leads to an increased rate of clearance and the

Table 3 *Euglobulin clot lysis time of venous blood samples taken from legs with and without venous congestion*

	Median (min)	Range (min)	Effect of congestion
Controls			
No congestion	241	112–380	$P<0{\cdot}01$
Congestion	126	51–264	
Varicose veins			
No congestion	195	95–291	
Congestion	32	15–85	
Healed ulcers			
No congestion	420*	88–540	n s.
Congestion	392†	61–540	

Compared with controls, * $P<0{\cdot}05$, † $P<0{\cdot}01$ (Mann–Whitney *U* test). n.s., Not significant

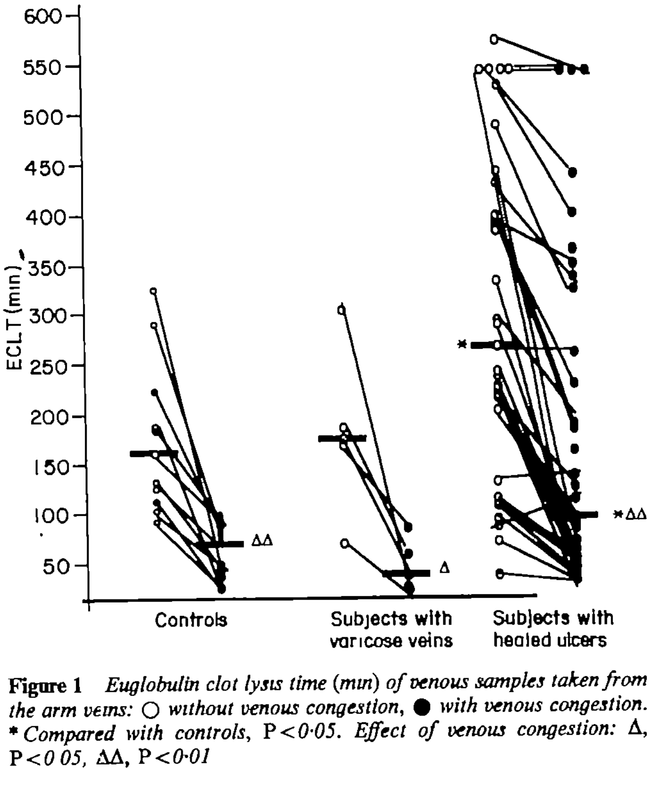

Figure 1 *Euglobulin clot lysis time (min) of venous samples taken from the arm veins:* ○ *without venous congestion,* ● *with venous congestion. * Compared with controls,* $P<0{\cdot}05$*. Effect of venous congestion:* Δ, $P<0{\cdot}05$, ΔΔ, $P<0{\cdot}01$

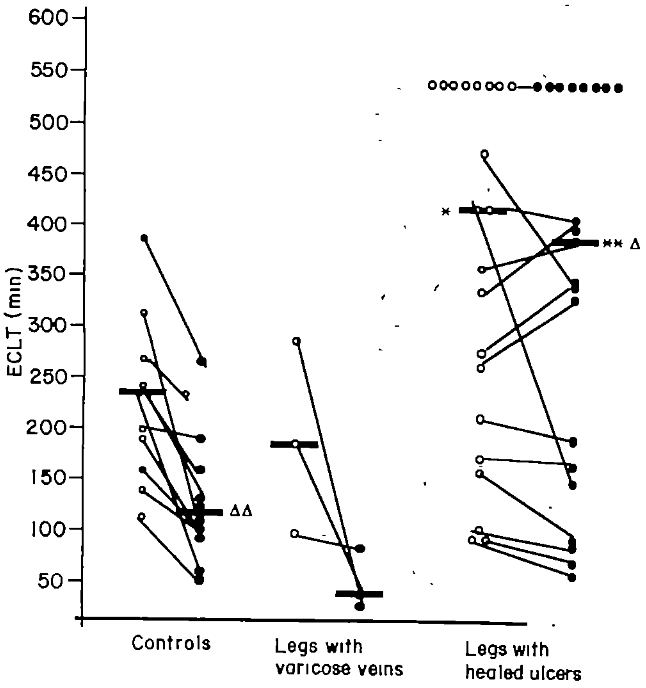

Figure 2 *Euglobulin clot lysis time (min) of venous blood taken from the leg veins* ○ *without venous congestion,* ● *with venous congestion Compared with controls,* *P<0·05, **P<0·01 *Effect of venous congestion* Δ, *n s.;* ΔΔ, P<0·01

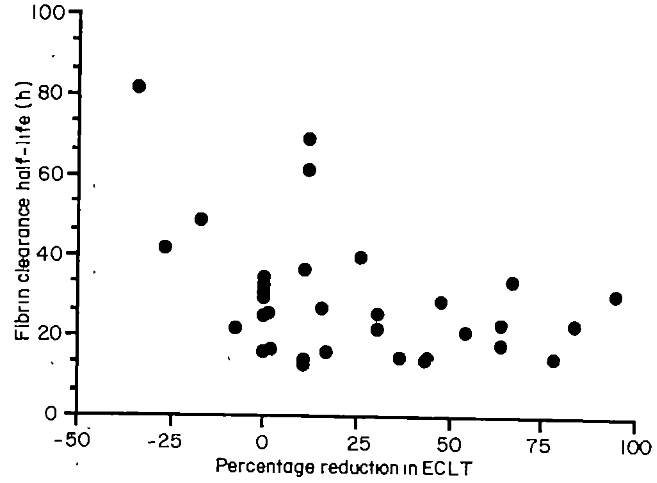

Figure 3 *Relationship between fibrin clearance half-life (h) from the legs and the percentage reduction in euglobulin clot lysis time of leg venous blood with venous congestion Spearman rank correlation coefficient* = −0·32 (P<0·05)

appearance of radioactivity in the fibrinogen fraction of the blood. These observations suggest that the fibrinogen is being altered and made less soluble[5]. Markwardt and Nowak[6] have also reported the use of localized radiolabelled microthrombi for studying fibrinolysis, and have reported changes in clearance rates in response to manipulating the fibrinolytic system.

The result of the clearance studies of ^{125}I-labelled human albumin, which was cleared much more quickly from the legs than from the arms, supports the conclusion that clearance of ^{125}I-labelled fibrin clots cannot be explained solely in terms of physical factors unrelated to fibrinolytic activity, such as blood and lymph flow. These findings also agree with other work which has shown that transit of relatively soluble subcutaneous proteins into lymph is more rapid from limbs with venous oedema than from controls[7,8]. Thus the evidence suggests that the injected fibrinogen is converted to fibrin and that its clearance depends on the fibrinolytic activity of the interstitial fluid. We acknowledge, however, that measurements of fibrin clearance and ECLT are not direct measurements of plasminogen activators. The results of the measurement of fibrin clearance half-life from the arms and legs suggest that there is diminished interstitial fibrinolytic activity in the legs of those with simple varicose veins and healed venous ulcers, compared with controls. Evidence from measurement of arm fibrin clearance also suggests that this impairment of interstitial fibrinolytic activity is not generalized, because the rates of fibrin clearance from arms of the controls, patients with simple varicose veins and patients with healed venous ulcers were not significantly different.

There may be some relationship between severity of the venous disorder and impairment in interstitial fibrinolytic activity. Clearance of fibrin was significantly longer in legs with healed ulcers compared with opposite legs which had never been ulcerated. Furthermore, clearance of fibrin from these two categories of limb was significantly longer than clearance in legs of controls.

These findings differ from those of the pilot study of Leach and Browse[9] who, using a similar technique for producing interstitial ^{125}I-labelled fibrin clots in six normal volunteers and six patients with lipodermatosclerosis, found the arm as well as the leg clearance to be significantly longer in patients with lipodermatosclerosis. They suggested that interstitial fibrinolytic activity was impaired in the arms and legs of patients with lipodermatosclerosis. However, the study involved only a small number of subjects, and the difference observed at 24 h between the arms of controls and those with lipodermatosclerosis was not present at 48, 72 or 96 h

The results described in the present paper come from a much larger number of subjects, using a technique that has been modified and improved Site and depth of injection have been standardized, activity at the injection site has been corrected for the natural decay of the isotope, and clearance half-life has been calculated from a series of measurements at the injection site taken over 4 days.

The ECLT of venous blood taken from legs was prolonged compared with that of blood taken from arms in both controls and those with healed venous ulcers, confirming previous results[10]. The ECLT of venous blood taken from arms and legs of those with healed venous ulcers was prolonged compared with that of blood taken from arms and legs of controls, which also confirms previous results[11,12]. However, the relationship between plasma ECLT, particularly its response to venous congestion, and interstitial fibrinolytic activity has not previously been investigated. The effect of venous congestion was to reduce plasma ECLT from all limbs except legs of those with healed venous ulcers. A statistically significant correlation was found between fibrin clearance half-life of all lower limbs and percentage reduction in the plasma ECLT of venous blood from the leg in response to venous congestion, even though fibrin clearance half-life did not correlate with absolute level of ECLT before or after venous congestion. It therefore appears that it is the response of veins to venous congestion, which is generally accepted as a measure of the ability of venous endothelium to release plasminogen activators, that determines interstitial fibrinolytic activity As much of the activator comes from the endothelium of the vena venorum, it is not unreasonable to assume that just as much diffuses outwards into the interstitial fluid as diffuses into the blood. This may explain why clearance of ^{125}I-labelled fibrin from arms of those with healed venous ulcers was not different from that of controls because, even though the ECLT of venous blood from arms was prolonged and vein wall activity was reduced, the ability to release activator in response to congestion was normal.

The present results suggest that chronic venous hypertension, the fundamental physiological abnormality of chronic venous insufficiency, reduces the ability of leg veins to produce plasminogen activator, an effect which is reflected in the fibrinolytic activity of the interstitial fluid as well as the blood. When the physiological abnormality is severe, the fibrinolytic activity of all the circulating blood is reduced, but the ability of the arm veins to release activator is not reduced. This suggests that the changes in arm vein blood and vein wall fibrinolytic activity are secondary to the disease in the legs, not a primary generalized venous abnormality. Unfortunately, our methods of measuring fibrinolytic activity are crude and subject to considerable variation. It is not possible to decide whether tissue response to venous insufficiency depends on the ability of venous endothelium to produce activator Not every patient with severe chronic venous hypertension develops lipodermatosclerosis. This study suggests that patients whose venous endothelium is unable to withstand the perpetual stimulus to produce plasminogen activator, perhaps because of an inherently low level of production or an inhibited production process, and consequently fail to produce sufficient activator to ensure that their interstitial spaces are cleared of fibrinogen/fibrin, may be the patients who develop ulcers.

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Time trends in incidence rates of acute, non-traumatic extremity ischaemia: a population-based study during a 19-year period

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Time trends in the occurrence of acute limb ischaemia were studied from 1965 to 1983 in a defined geographical area in Sweden. Data were obtained from a computerized register which covers all instances of inpatient care for a population of 1·3 million. Analysis based on 5394 first admissions for acute arterial occlusion revealed that the annual number increased by 2·7 per cent yearly in women and 3·9 per cent in men whereas the age-adjusted incidence remained stable for women and increased by 2·6 per cent yearly for men. A study of 1189 patients who underwent surgical procedures showed that the annual number of embolectomy procedures increased 7·6 per cent for females and 8·6 per cent for males. The corresponding age-adjusted incidence rose annually by 3·0 per cent for women and by 7·5 per cent for men. The introduction of the Fogarty catheter and an increasing interest in vascular sugery may have contributed to the increasing rates of operations during the period of study.

Acute arterial occlusion in the extremities presents a serious threat to life and limb with mortality figures ranging from 15–60 per cent, and limb loss occurring in 15–50 per cent after operative intervention[1–4]. In the last 30 years a tendency towards relatively more thromboses and fewer embolic episodes has been noted[1,3,5]. One explanation of this trend may be a fall in the prevalence of rheumatic heart disease with associated embolism of cardiac origin[3,6]. Concomitantly, the prevalence of all forms of arteriosclerotic vascular disease has increased (B. Tibell, thesis, 1970), partly because of the increasing life expectancy of the population in Western countries. Such trends may explain why the mean age of patients with acute arterial occlusion has risen from around 60 years to more than 75 years in many reports[5–7].

Published studies of patients with acute extremity ischaemia – amounting to more than 50 in 1988 – are based on a selection of patients, who have usually been examined in university departments with a special interest in vascular surgery. The incidence rates in a defined population have never been adequately investigated. In one small Swedish series, the crude rate of acute arterial occlusion of the extremities was estimated at 9 per 10^5 person-years, with a low incidence at younger ages (0·4 in the age group 20–30 years), but rising to about 180 per 10^5 above 90 years of age[8]. However, further population-based data are lacking

The aim of this study was to report the incidence figures for acute non-traumatic arterial ischaemia and operative procedures performed for this condition in a large population, and to analyse time trends during a 19 year period By using the Swedish inpatient register covering all somatic inpatient care from 1965 to 1983 in a population of about 1·3 million (1970) we have defined one cohort based on diagnoses by physicians during inpatient care and one based on operative procedures due to acute arterial occlusion.

Materials and methods

The Inpatient Register (IPR)

The data used in this study were obtained from a computerized register, the IPR, maintained by the Swedish National Board of Health and Welfare (NBHW) The NBHW received annual reports on individual hospital admissions and discharges in the Uppsala healthcare region from 1965 to 1983 This region had a total of about 1·4 million inhabitants in 1983, approximately 16 per cent of the total population of Sweden (NBHW statistics, 1984)

In addition to the individually unique National Registration Number each record contains data on domicile, dates of admission and discharge, hospital department of admission, diagnoses and operations. The diagnoses are codified according to the Swedish revision of the International Classification of Diseases (ICD) For 1965–1968 the seventh edition of ICD was used (NBHW statistics, 1965), and from 1969 onwards the eighth edition (NBHW statistics, 1968).

Overall, about 2 per cent of the total number of discharges had not been included in the register (NBHW statistics, 1969, 1984), but disproportionately low counts of total admissions were found for three counties in one to four specific years (NBHW statistics, 1984) Consequently figures from these counties and years were omitted from the analyses The excluded material comprised 4 per cent of the total 'person-years' in the region during the study period

A number of checks such as logical correctness in the dates of birth, admission and discharge, and codes for county and community of residence were made of the IPR records for admissions due to acute arterial thrombosis or embolism. These yielded valid data in 99·2 per cent of all records in which a correct nine-digit National Registration Number was available

The diagnosis cohort

All inpatient cases given a discharge diagnosis of acute arterial thrombosis or embolism during the period 1965–1983 were compiled from the register, whether or not a surgical intervention was carried out The total number of first recorded admissions with this diagnosis was 5394; 2642 men and 2752 women The diagnosis was made predominantly in the departments of internal medicine (48 per cent), surgery (33 per cent) and geriatrics (11 per cent)

In order to check whether the ICD-7 code was erroneously used for acute arterial occlusion even after 1968, all 5326 patients given ICD code 454 00 after 1969 were scrutinized for the occurrence of a surgical procedure code indicating that an embolectomy had been performed Only one miscoding was discovered. A further check was carried out on hospital records of 53 patients, a random 1 0 per cent sample of all patients, but none with an acute arterial extremity ischaemia was found The national registration number, sex, date of admission and discharge, second and third diagnostic codes and surgical procedure codes were also found to be in accordance with register data

The correctness of the ICD code (i e. the positive predictive value)

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was checked in hospital records from 536 patients, a random 10 per cent sample. This review revealed a miscoding of the diagnosis in 139 cases (25·9 per cent); most of them (123 patients) had deep venous thrombosis or pulmonary embolism. Apart from the first 4 years when the miscoding rate was low (less than 10 per cent), no time trends were apparent in the annual miscoding rate.

The operated cohort

All inpatient events among residents of the Uppsala health care region with a first discharge record including a surgical procedure code for thrombectomy or embolectomy during the period 1965–1983 (a total of 1574) were compiled from the register. Among them 385 inpatient events were found for which the diagnosis did not accord with the description of spontaneous acute arterial occlusion, or there was lack of accord between the embolectomy code and the card ICD diagnosis. A check revealed that no patient in this group met the criteria for inclusion in the study group, mainly due to embolectomy as part of a reconstructive procedure (82 cases), thrombotic complications secondary to angiography (55 cases), or erroneous coding of venous embolectomy (90 cases). Thus there remained 1189 individuals (647 women and 542 men) to constitute the definite cohort.

A validity check on 122 records, a random 10 per cent sample of the final surgical procedure cohort of 1189 first admissions, revealed that in two cases (1·6 per cent) venous thrombectomy was miscoded as an arterial embolectomy procedure, in eight cases (6·6 per cent) an operative procedure was performed on the upper extremity and in six cases (4·9 per cent) the patient card was missing.

Statistical methods

Population figures from the Uppsala health care region, classified by gender and 10 year age group, were obtained for each year of the study. Age-standardized rates were determined using the direct method of adjustment[9], with the Swedish population census in 1970 as the standard population[10]. Statistical analysis of time trends were performed using a semilogarithmic model based on yearly incidence figures which assumed a constant change in incidence rates during the study period[17]. The χ^2 test was used to test differences between the sexes and different age-groups.

Results

The diagnosis cohort

The age distribution differed between the sexes ($P=0{\cdot}04$) with 72·0 per cent of cases occurring at age 70 or older in women and 56·8 per cent in men. Conversely, men predominated in the sixth decade, with 11·0 per cent of cases compared with 6·7 per cent of women and in the seventh decade the corresponding figures were 25·5 per cent compared with 16·3 per cent (*Table 1*). An analysis of the age-specific incidence per year for the whole study period revealed higher rates in men than in women below age 70, and an exponential increase with virtually identical slopes for both sexes (*Figure 1*).

The annual number of first admissions increased steadily and highly significantly in both sexes over the study period ($P=0{\cdot}0001$), in women from 104 in 1965 to 167 in 1983 and in men from 98 to 176 over the same period. On average the in men. The age-adjusted incidence rates displayed no definite time trend in women ($P=0{\cdot}65$), but rose in men on average by 2·6 per cent yearly ($P<0{\cdot}001$) (*Figure 2*). Consequently there was a slight decrease in the female:male ratio of annual age-adjusted rates during the study period.

There was no evidence in women of a change in the age-specific incidence, except in the age group 80 years and older, in which the rate increased by 1·8 per cent yearly from 216 per 10^5 in 1965 to 290 per 10^5 in 1983 ($P=0{\cdot}007$). Likewise the age-specific incidence among men in the oldest age group rose from about 160 per 10^5 in 1965 to about 290 per 10^5 in 1983 ($P=0{\cdot}002$), but there was also a slight increase over the study years in the ninth decade ($P=0{\cdot}006$), from 85 per 10^5 in 1965 to 120 per 10^5 in 1983 and in the eighth decade from 90 in 1965 to 130 in 1983. The variation was greater in the oldest age groups, reflecting random variation due to the lower population figures.

The operated cohort

Of the 1189 patients 80·2 per cent of women and 67·7 per cent of men were 70 years or older (*Table 2*). The age-specific incidence rates per year for the entire study period (*Figure 3*) revealed essentially the same patterns as for the diagnosis cohort, but the sex difference was less pronounced. In the group

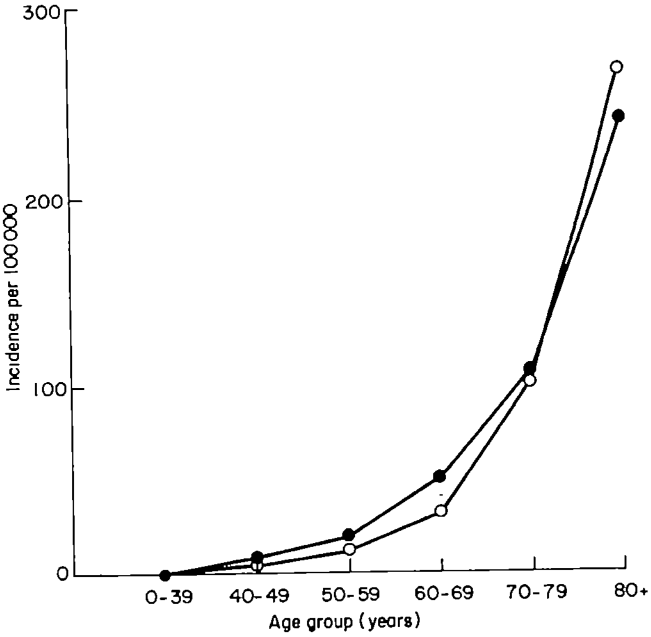

Figure 1 *Diagnosis cohort. Age-specific incidence rates for the period 1965–1983.* ●, *Men,* ○, *women*

Table 1 *Number and age-specific incidence × 10^5 patients diagnosed as having acute arterial occlusion in the Uppsala healthcare region, Sweden, in 1965–1983, by gender and 10-year age group*

Age (years)	Women			Men		
	Number	Percentage	Annual incidence	Number	Percentage	Annual incidence
<40	62	2·3	0·9	64	2·4	0·9
40–49	73	2·7	5·2	115	4·4	8·5
50–59	185	6·7	12·6	290	11·0	19·5
60–69	448	16·3	32·9	672	25·5	51·2
70–79	967	35·1	101·3	863	32·7	107·8
80–89	884	32·1	266·8	566	21·4	240·1
>90	133	4·8	–	70	2·7	–
All	2752	100·0		2640	100·0	

over 80 years of age, the incidence rate for women was 64 per 10^5 and 75 per 10^5 for men.

There was a marked increase in the average annual number of procedures performed in women, 7·6 per cent yearly ($P<0{\cdot}001$). The increase was of the same magnitude in men, 8·6 per cent every year ($P<0{\cdot}001$).

In women the age-adjusted incidence rose on average by 3·0 per cent yearly ($P=0{\cdot}005$). Among men the trend appeared stronger, with approximately 7·5 per cent yearly increase ($P<0{\cdot}001$) (*Figure 4*). Therefore, as with the diagnosis cohort, there was a decrease in the female:male ratio of age-adjusted rates during the study period.

Age-specific incidence rates for women increased threefold in the oldest age group, from 35 per 10^5 in 1965 to 105 per 10^5 in 1983 ($P<0{\cdot}001$). There was also a 50 per cent rise over the study period in the 70–79-year age group, from 20 per 10^5 in 1965 to 30 per 10^5 in 1983 ($P=0{\cdot}07$). The same tendency applied to men, with a more than fivefold rise in the group above 80 years of age (from 18 per 10^5 in 1965 to 100 per 10^5 in 1983 ($P<0{\cdot}001$), and about a 6·3 per cent yearly increase in the eighth decade (from 20 per 10^5 in 1965 to 36 per 10^5 in 1983 ($P=0{\cdot}001$).

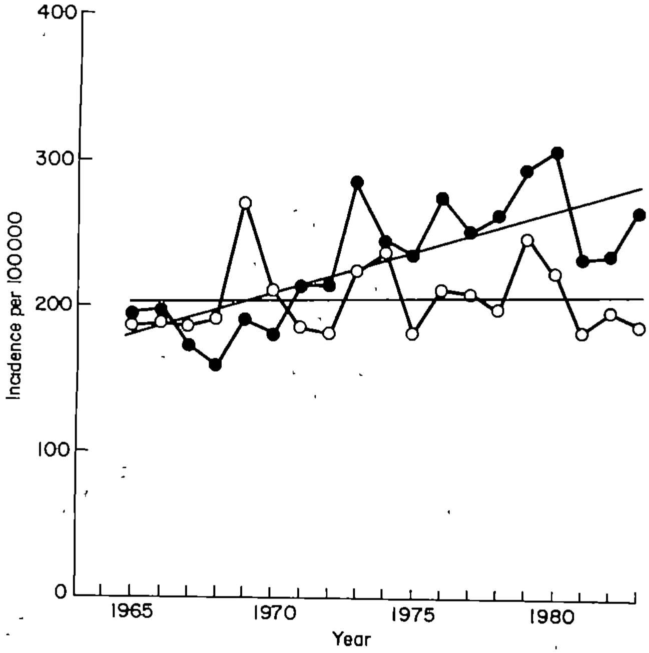

Figure 2 *Diagnosis cohort. Age-adjusted incidence rates of diagnosed arterial occlusions per year for the period 1965–1983.* ●, *Men,* ○, *women*

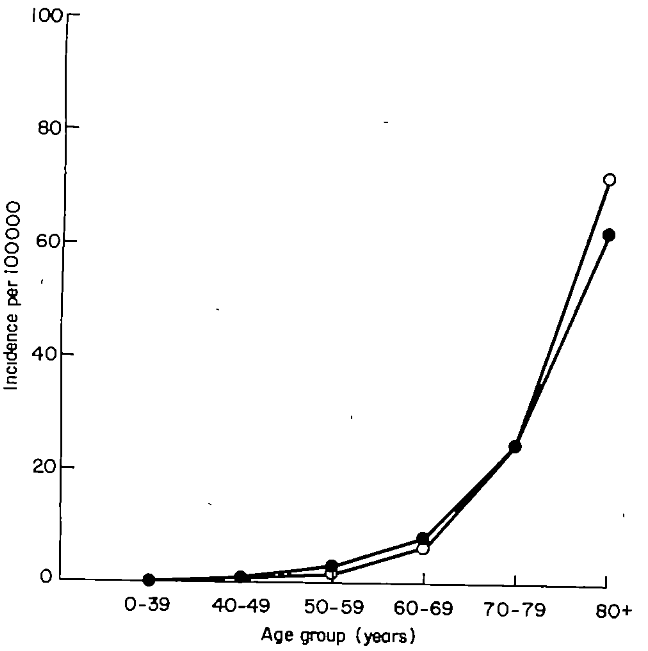

Figure 3 *Operated cohort. Age-specific incidence rates for the period 1965–1983.* ●, *Men,* ○, *women*

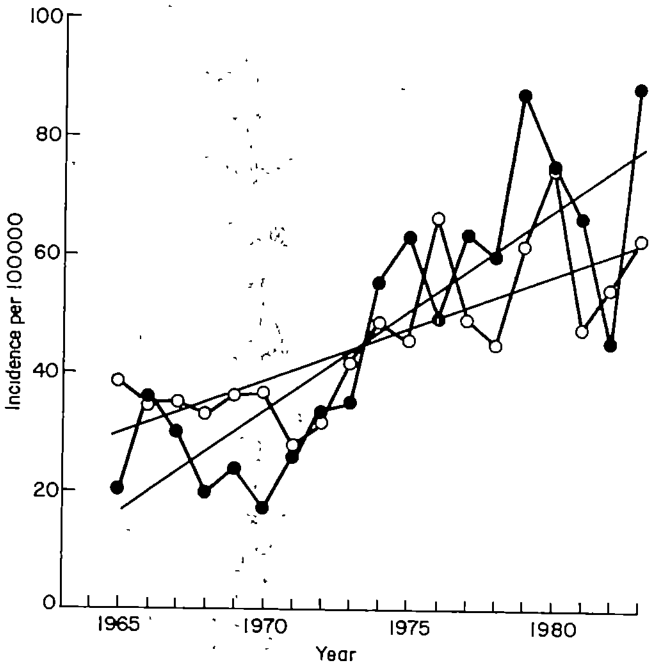

Figure 4 *Operated cohort. Age-adjusted incidence rates of performed operations for acute arterial occlusions per year over the period 1965–1983.* ●, *Men,* ○, *women*

Table 2 *Number and age-specific incidence* $\times 10^5$ *of patients operated on with thrombectomy or embolectomy in the Uppsala healthcare region, Sweden, 1965–1983, by gender and 10-year age-group*

Age (years)	Women			Men		
	Number	Percentage	Annual incidence	Number	Percentage	Annual incidence
<40	3	0·5	0·0	9	1·7	0·1
40–49	10	1·5	0·7	14	2·6	0·9
50–59	25	3·9	1·6	44	8·1	2·9
60–69	91	14·0	6·6	108	20·0	8·2
70–79	234	36·1	24·5	200	37·0	25·0
80–89	247	38·1	72·3	145	26·8	62·6
>90	39	6·0	–	21	3·9	–
All	649	100·0		541	100·0	

Discussion

Few attempts to study basic descriptive epidemiology of acute arterial ischaemia in the extremities have been published[8,11]. The computerized inpatient register provided large numbers and nearly complete statistics concerning hospital admissions for acute arterial ischaemia For inpatient care there existed no alternative to county hospitals run by county authorities in this area. All patients with a sudden onset of ischaemia were likely to be admitted to inpatient care.

Some methodological aspects require consideration. Miscoding meant that in the diagnosis cohort about 25 per cent of patients were treated for deep venous thrombosis or pulmonary embolism. This figure was apparently constant over the study period, indicating that the trends in the annual number of admissions of men and women and that the rising age-adjusted incidence rates for men were real. The differing trends in the age-adjusted incidence rate of men and women support this conclusion, since it is unlikely that miscoding could have affected the sexes differently during the study period.

In the diagnosis cohort, the admission date in geriatric wards may precede the acute arterial occlusion by months and even years. However, less than 11 per cent of first admission diagnoses were made in geriatric wards and less than 3 per cent of patients had a hospital stay of more than one year

In the operated cohort, we found little evidence that miscoding or other methodological flaws could have biased the incidence rates. It may be assumed, therefore, that the present data are valid for studying incidence rates and time trends for patients with acute arterial occlusion, and particularly for surgical procedures undertaken for this condition.

For both cohorts the age-standardized rates increased throughout the study, most markedly among men in the operated cohort. Age-specific analyses revealed, however, that the increase was largely confined to individuals of 70 years or older. A plausible explanation of this trend may be wider indications for surgery during the latter part of the study period. A similar increase in incidence of surgical intervention has been reported from Boston[6]. The beginning of the study period coincided with the introduction of the Fogarty catheter, a technical achievement that simplified embolectomy and may have contributed to the increasing incidence of surgery undertaken for acute arterial occlusion. It is noteworthy, however, that the introduction of this new technique did not seem to have any beneficial influence on the mortality or amputation frequency after embolectomy[1,6,11].

The only published analysis on the incidence of acute arterial embolism and thrombosis[8] showed substantially lower incidence rates than the present study, e.g. 180 per 10^5 above 80 years of age compared with 266 per 10^5 for women and 240 per 10^5 for men in our analyses. A comparison with the study by Dryski and Swedenborg[12] is difficult, since their work focused on the result of treatment and provided no estimates of incidence rates.

Acute, non-traumatic arterial occlusion due to thrombosis is a late manifestation of arteriosclerotic vascular disease. The crude rate should therefore increase with increasing numbers in the highest age groups in the population, reflecting increasing life expectancy. However, even after age adjustment the present data indicated a rise in incidence rates in men over the study years. If this trend is true, one explanation may be sought in the increasing exposure to life style factors that promote arteriosclerotic disease in the birth cohorts that reached their eighth and ninth decades during the study period. Throughout the last 50 years smoking has increased in western countries, parallelling the rise in economic standard. During the same period smoking-related morbidity, such as that from lung cancer and cardiovascular disease, has increased dramatically.

Concomitant with this rising incidence of acute arterial occlusion, the age at diagnosis has risen[5–7], and a tendency towards an increase in the ratio of arterial thrombosis to embolism has been noted by several investigators[1,3,4]. These findings have been confirmed by vascular units and are thought to be due to a fall in the prevalence of rheumatic heart disease[1,3,13,14] which, until 1970, was the primary cause of peripheral arterial embolism[3]. Advances in cardiological medical care with a more effective prevention of embolism (treatment for atrial fibrillation and anticoagulation) is a reasonable explanation for decreasing rates of arterial embolism. However, published series are retrospective and do not form conclusive evidence for the presence of a definite trend towards increasing incidence of thrombosis at the expense of embolism Data supporting different treatments in cases of embolism and thrombosis are accumulating[14] so this diagnostic challenge is important. The present data were not sufficiently detailed for a separate analysis of thrombosis and embolism, and considering that a retrospective analysis would have to rely on a subjective diagnosis, the validity of such an exercise is doubtful. The only valid means of studying this issue is a prospective study.

In view of the very grave prognosis for this disease and the marked increase in the number of cases, more research on surgical intervention and anticoagulation, and on new therapeutic approaches such as thrombolytic therapy, should be carried out.

Acknowledgements

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Realistic expectations for the patient with intermittent claudication

To determine the natural history of intermittent claudication 112 patients were followed for a minimum of 5 years and a median period of 82 months. Thirty-seven patients (33 per cent) died during the study period. Myocardial infarction (44 per cent) and cerebrovascular disease (28 per cent) were the most common causes of death. Overall mortality rate was 8, 23 and 40 per cent, at 2, 5 and 8 years respectively. Initial ankle–brachial pressure index (ABPI) correlated with subsequent death. With an initial ABPI <0·5 death occurred in 20, 50 and 69 per cent at 2, 5 and 7 years respectively, compared with 5, 16 and 24 per cent respectively for those with an initial ABPI ⩾0·5 (P<0·0001). *Of the survivors only 21 per cent had worsening claudication and 13 per cent progressed to critical ischaemia. Arterial bypass for limb salvage was required in eight patients and four limbs were lost during the study period. ABPI identifies a subgroup of claudicants with an extremely high risk of death from coronary and/or cerebral pathology. In this subgroup an aggressive approach to the correction of atherosclerotic risk factors, rather than emphasis on the peripheral vascular problem alone, may improve survival.*

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Much of our understanding of the natural history of mild peripheral vascular disease is based on the classical work of Boyd and Bloor in the 1950s[1,2] and other studies early in the history of vascular surgery[3–6]. While intermittent claudication was reported to have a high associated mortality rate, the prognosis for the affected limb was relatively benign. Nevertheless, Rosenbloom *et al.* recently reported that 41 per cent of claudicants progressed to critical ischaemia at 8 years[7].

The present study of conservatively treated patients with intermittent claudication was performed to delinate further the natural history of this condition in the 1980s, in terms both of survival and of progression of peripheral ischaemia, and to identify any risk factors that are predictive of outcome. Identification of patients at high risk of death or limb loss should assist therapeutic decision making.

Patients and methods

Patients were selected for this study if they had both intermittent claudication and either an ankle–brachial pressure index (ABPI) <0·85 at rest or a 15 per cent decrease in ABPI on exercise. Those with rest pain, ulceration, gangrene or whose initial treatment was surgical were excluded A total of 113 consecutive patients who presented between 1981 and 1983 and fulfilled these criteria were followed for a minimum of 5 years and a median period of 82 months; one patient was lost to follow-up. At initial and subsequent assessments all patients had full clinical evalutaion and non-invasive vascular studies including the measurement of ABPI. Using a Doppler ultrasound probe as a flow sensor, systolic pressure was measured in the dorsalis pedis, posterior tibial and peroneal arteries in both ankles The highest of these three pressures was divided by the higher of the two brachial systolic pressures to calculate the ABPI ABPI in the more severely affected leg was used for correlation with subsequent patient survival. Risk factors including serum cholesterol and triglycerides, smoking habits and hypertension were assessed and, where appropriate, patients were advised about their correction.

The two end points were death, and progression to critical ischaemia as defined by the Working Party of the International Vascular Symposium[8]. Results were calculated using life table analysis. Life table curves were compared using the generalized Wilcoxon/Breslow statistic. The comparative significance of multiple variables on subsequent outcome was estimated with a stepwise linear regression technique based on the Cox proportional hazards model Mortality rates for an age and sex matched population are based on World Health Organization figures for mortality in Ireland[9]

The mean patient age was 61 6 years (range 40–80) and the male:female ratio was 3:1. Atherosclerotic risk factors in the study population included smoking (90 per cent), hypercholesterolaemia (39 per cent), hypertension (14 per cent) and diabetes (4 per cent)

Results

Thirty-seven deaths occurred during the study period. The mortality rate was 8, 23 and 40 per cent at 2, 5 and 8 years respectively; double that of an age and sex matched population (*Figure 1*). The most common causes of death were ischaemic heart disease (44 per cent) and cerebrovascular disease (28 per cent).

Multivariate analysis identified initial ABPI as a predictive factor for death (P<0·005); the lower the ABPI the higher the mortality rate. 25 Per cent of patients had an ABPI <0·5 This subgroup had a mortality rate of 20, 50 and 69 per cent at 2, 5 and 7 years respectively compared with 5, 16 and 24 per cent respectively for those with an initial ABPI ⩾0·5 (*P*<0·0001) (*Figure 2*). Mortality rate for those with an initial ABPI ⩾0·5 was little higher than that for an age and sex matched population (*Figure 2*). No other risk factor examined predicted survival: age (*P*=0·10), level of arterial occlusion (*P*=0·16), serum cholesterol (*P*=0·44), hypertension (*P*=0·48), smoking (*P*=0·59), and sex (*P*=0·64).

Of the survivors, 66 per cent were symptomatically improved or stable, 21 per cent had a shortened claudication distance and 13 per cent had progressed to critical ischaemia at the end of the study period. Progression to critical ischaemia occurred in 6, 9 and 12 per cent of patients at 2, 5 and 8 years respectively (*Figure 3*) During the study period eight patients had reconstructive surgery for limb salvage and seven for debilitating claudication. Four limbs were lost, one following occlusion of a peripheral bypass graft and three in two non-reconstructable diabetics. Of the variables examined only

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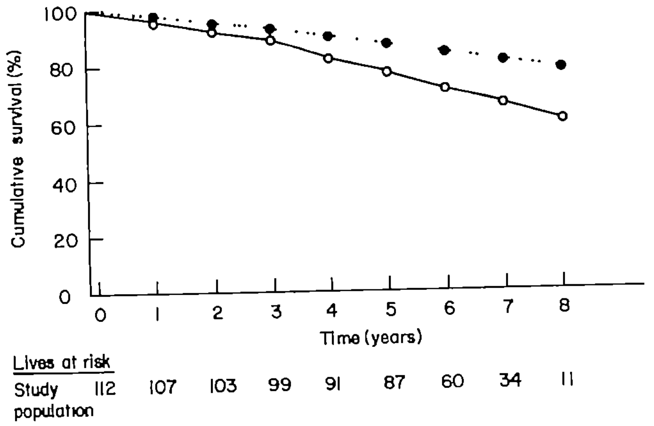

Figure 1 *Cumulative survival of the study population compared with that of an age and sex matched population.* ●, *Matched population,* ○, *study population. Numbers indicate the number of patients at risk at various times*

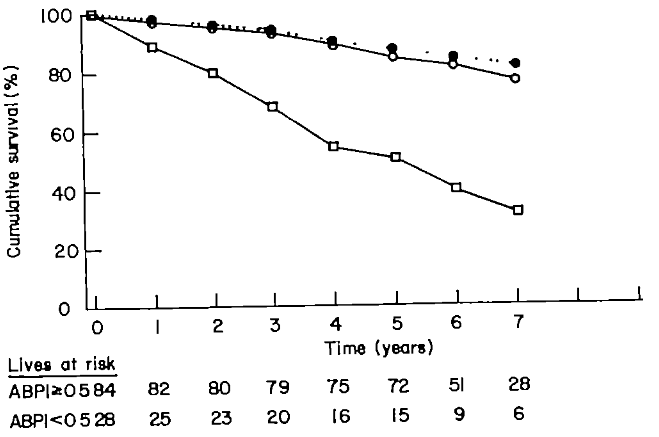

Figure 2 *Cumulative survival of patients with an initial ankle–brachial pressure index (ABPI) ≥0·5 compared with those with an ABPI <0·5 (P<0·0001). The survival curve for an age and sex matched population is shown.* ●, *Matched population;* ○, *ABPI ≥0·5,* □, *ABPI <0·5. Numbers indicate the number of patients at risk at various times*

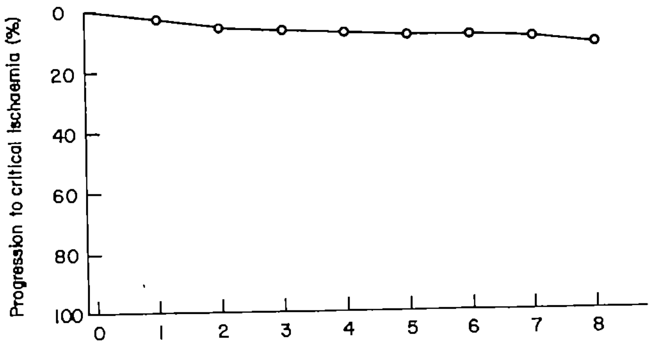

Figure 3 *Cumulative rate of progression to critical ischaemia in the study population. Numbers indicate the number of patients at risk at various times*

age predicted progression to critical ischaemia ($P = 0{\cdot}028$), while smoking at the outset ($P = 0{\cdot}08$) and continued smoking during the study period ($P = 0{\cdot}10$) approached statistical significance. Non-predictive factors included level of arterial occlusion ($P = 0{\cdot}34$), hypertension ($P = 0{\cdot}4$), initial serum cholesterol ($P = 0{\cdot}5$), sex ($P = 0{\cdot}52$) and initial ABPI ($P = 0{\cdot}53$).

At final assessment 57 per cent of original smokers continued to smoke. Mean reduction of serum cholesterol was only 1·8 per cent in spite of dietary advice; 37 per cent of patients had hypercholesterolaemia.

Discussion

Although often considered a benign condition, intermittent claudication in this study had a high associated mortality rate, the most frequent causes of death being ischaemic heart disease and cerebrovascular disease. The overall mortality rate, double that of a matched population, was similar to those of previous reports[1,10–12]. The identification of ABPI, a simple and readily measurable index, as the most important predictive factor for death in patients with intermittent claudication, and the finding that those with an ABPI <0·5 have a particularly malignant prognosis, have important clinical implications. In patients with a low ABPI, diversion of attention to mortality risk rather than focusing on the local peripheral vascular problem alone may result in improved survival. On the other hand patients with an ABPI significantly above 0·5 can be reassured that their risk of death differs little from that for the population at large, matched for age and sex. No previous study of claudicants has identified a more powerful predictor of death

Death risk can be influenced by correcting blood cholesterol[13,14], smoking habit[15] and hypertension[16]. The LRC–CPPT trial[17] and Helsinki Heart Study[18] both demonstrated a reduction in death from ischaemic heart disease after pharmacological lowering of cholesterol in hypercholesterolaemic patients. These trials, however, both contained patients without known atherosclerotic disease, and how applicable their data are to claudicants is unknown. While no good data exists on the reduction of mortality rate in claudicants, secondary prevention has been addressed in patients with established ischaemic heart disease, a comparable population in many respects. Two studies have shown a significant reduction in mortality rate after pharmacological lowering of cholesterol in survivors of myocardial infarction[19,20]. This suggests that identification of claudicants with a high risk of death, followed by an aggressive approach to the correction of their atherosclerotic risk factors, may result in significant improvement in survival, principally through a reduction in cardiac deaths.

The long held view that intermittent claudication has a benign prognosis in terms of progression of *peripheral* vascular disease was confirmed in this study. Only 12 per cent progressed to critical ischaemia at 8 years, 13 per cent had revascularization, and only four limbs were lost. These results are in keeping with most previous reports[1–4,21,22] but contrast with the 41 per cent rate of progression to critical ischaemia at 8 years reported by Rosenbloom and colleagues[7]. The reason for this difference is unclear though 34 per cent of patients in that study were diabetic compared with 4 per cent in the present study. Only age and continued smoking appeared to correlate with progression to critical ischaemia though smoking did not reach statistical significance. In this study initial ankle blood pressure, contrary to the report of Jelnes *et al.*[11], did not predict progression to critical ischaemia.

This study has confirmed the high risk of death associated with intermittent claudication and has defined a large and readily identifiable subgroup of patients for whom the risk is especially pronounced. On the other hand the relatively benign prognosis in terms of progression of peripheral ischaemia has been confirmed. Identification of patients at high risk of death followed by an aggressive approach to the correction of their atherosclerotic risk factors may improve survival in those with intermittent claudication.

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Epidemiology of chronic venous ulcers

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A metropolitan population of 238 000 in Perth, Western Australia, was screened for chronic ulceration of the leg. Patients with a chronic leg ulcer and a venous abnormality comprised 57 per cent of all patients with a chronic leg ulcer, giving a prevalence of 0·62 per 1000 population. There was an increasing prevalence with age; 90 per cent of patients were 60 years and older. This group comprised 16·7 per cent of the population, and had a prevalence of 3·3 per 1000. Although chronic venous ulcers were more common in women there was no difference in age related prevalence. In 36 per cent of patients with a venous abnormality, there was at least one other aetiological factor contributing to chronic ulceration of the leg; 96 per cent had either a history of deep venous thrombosis or a condition known to predispose to deep venous thrombosis.

Chronic venous ulceration is frequently encountered in clinical practice; however, little information is available about its prevalence and natural history. This information can only be reliably obtained by screening a large population for chronic ulceration of the leg, and further examining a representative sample to identify those with a venous abnormality.

Existing published data from population based studies has focused on leg ulcers of heterogeneous aetiology. Two studies have examined small European populations, and suggest that about 1 per cent of people have leg ulcers at some time. Active or healed leg ulcers were found in 153 of 15 060 adults surveyed by Bobek *et al.*[1], and in 46 of 4529 adult factory workers studied by Widmer[2].

Two reports from large populations in the United Kingdom enable the prevalence of venous ulcers to be derived. In a postal survey of the Lothian and Forth Valley Health Districts, with a population of about one million, Callam *et al.*[3] found the prevalence of chronic leg and foot ulcers to be 1·48 per 1000 population. In 600 patients 827 ulcerated limbs were examined clinically, and venous disease was diagnosed in 76 per cent of legs[4]. If this proportion of patients in the study area had a venous ulcer, the prevalence of venous ulceration would be 1·12 per 1000 population.

Cornwall *et al.*[5] studied a health district with a population of about 200 000. The prevalence of leg ulcer (isolated ulceration of the foot was excluded) was 1·8 per 1000 population. In 100 patients 117 ulcerated limbs were examined; venous disease was diagnosed by photoplethysmography in 81 per cent of limbs. Assuming the same proportion of all patients had venous ulcers, the prevalence of venous ulceration would be 1·46 per 1000 population. (When the study was repeated 18 months later, the prevalence of leg ulcers had fallen to 1·1 per 1000 population, with a derived figure for venous ulcers of 0·89 per 1000 population. The change was attributed to improved treatment.)

In this study a large metropolitan population was examined to determine the prevalence and clinical characteristics of chronic venous ulceration. Venous disease was identified with photoplethysmography.

Patients and methods

A Perth metropolitan population of 238 000 located south of the Swan River was studied. Demographic data were provided by the Australian Bureau of Statistics (Catalogue No. 3203.7 Estimated Resident Population Western Australia 30 June 1988).

Patient accrual was by referral from health professionals and institutions in the study area, and by self-referral. Following an introductory letter, a personal visit was made to all general practitioners, relevant medical specialists, podiatrists, directors of nursing homes, and Silver Chain (District) nurses in the study area to explain the purpose of the study and to provide information about the mechanism of referral. Self-referral was facilitated by publication of an article describing the study in local newspapers at the beginning of the recruitment period. Patients were recruited to the study over 3 months from 1 March to 31 May 1989.

For this study chronic ulceration of the leg was defined as a defect in the dermis at a site below the knee, persistent for 1 month or longer. An attempt was made to contact each patient entered into the study to undertake a detailed history and assessment of the cause of ulceration. Most patients were seen at their home, and some were seen at the Vascular Laboratory at Fremantle Hospital. The history included enquiry about the duration of the current ulcer, and the chronicity of ulceration. Specific enquiry was made for a past history of venous thrombosis, pulmonary embolus, events predisposing to venous thrombosis (limb trauma, general anaesthesia, and pregnancy), previous venous surgery, diabetes mellitus, rheumatoid arthritis, hypertension, and peripheral arterial disease. Patient mobility was graded as follows: Grade 1 – unrestricted, Grade 2 – limited mobility beyond the home; Grade 3 – housebound, Grade 4 – mobile with walking aid; Grade 5 – chairbound.

The ulcerated legs were examined, and the side of ulceration and the status of the pedal pulses were recorded. The site of ulceration was recorded using the method of Callum[4]. Zone 1 – the foot, Zone 2 – the gaiter area extending from 2·5 cm below the malleoli to the point where the calf muscles become prominent posteriorly; Zone 3 – extending above this to the knee.

To assess the cause of ulceration all patients had venous refilling assessed by photoplethysmography, using a Parks® Vascular Minilab 3 (Model 1059, Parks Medical Inc., Beaverton, Oregon, USA), according to the method of Abramowitz *et al.*[6]. With this apparatus we have found that 61 of 62 patients (98 per cent) with venous ulceration have a refilling time less than 25 s, while 119 of 122 patients (97·5 per cent) with no history of venous disease or leg ulceration have a refilling time greater than 25 s. If unable to flex the ankle adequately, the patient sat with the ulcerated limb dependent and unsupported. The calf was manually compressed eight times and venous refilling was recorded. Venous disease was considered to be part of the ulcer aetiology when there was an abnormal venous refilling time of less than 25 s on photoplethysmography in a limb with a chronic leg ulcer.

The resting arterial Doppler ankle·brachial pressure index was measured, and significant arterial ischaemia was considered to be present[7] when the index was less than 0·9. In patients with diabetes mellitus, who may have incompressible arteries, the absence of pedal pulses was also taken to indicate significant ischaemia. The following haematological data were also measured: urea, creatinine, random blood glucose, rheumatoid serology (rheumaton and latex tests) and autoantibody studies (antinuclear, antiparietal cell, antismooth muscle, and antimitochondrial antibodies).

Patient and ulcer variables were compared with χ^2 tests

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Results

The study accrued 259 patients with chronic ulceration of the leg; 242 patients (with 286 ulcerated limbs) were fully assessed using the method outlined and 17 were unavailable for full assessment An abnormal venous refilling time on photoplethysmography was found in 138 patients (with 163 ulcerated limbs), representing 57 per cent of the patients who were fully assessed. Assuming that the 242 patients assessed are representative of the whole 259 patients referred, the prevalence of chronic venous ulceration in this study population was 0·62 per 1000. In this paper the features of only the 138 patients with abnormal venous refilling time are described.

If patients with ulceration confined to the foot (Zone 1) are excluded, as was done in the study by Cornwall *et al.*[5], there were 222 patients of whom 204 (with 239 ulcerated limbs) were fully assessed; 136 of these patients (with 160 ulcerated limbs) had an abnormal venous refilling time (67 per cent of those fully assessed).

Age and sex distribution

The median age of patients with chronic venous ulcer was 75 years (range 20–99 years). There were 49 men and 89 women, (male·female ratio of 1:1·8). This difference was statistically significant ($\chi^2 = 9{\cdot}31$, $P < 0{\cdot}01$) but the female predominance occurred only in patients over 70 years old (*Table 1*). In this age group there is also a female predominance in the general population, and the prevalence of chronic venous ulcer for men and women was almost identical ($\chi^2 = 0{\cdot}909$, $P = 0{\cdot}34$). Indeed, prevalence was similar for men and women at all ages (*Table 1*).

The prevalence of chronic venous ulceration increased progressively with age (*Figure 1*). Ninety per cent (124) of patients with chronic venous ulcer, and 16·7 per cent of the population were over 60 years old. The prevalence in this subset was 3·3 per 1000 population

Table 1 *Prevalence of chronic venous ulcer related to age and sex of 138 patients*

Age (years)	Men		Women	
	Number	Prevalence per 1000	Number	Prevalence per 1000
0–39	1	0·015	2	0·029
40–49	0	0·0	2	0·15
50–59	4	0·38	5	0·46
60–69	13	1·5	13	1·3
70–79	16	3·3	29	4·0
80+	15	8·3	38	9·1

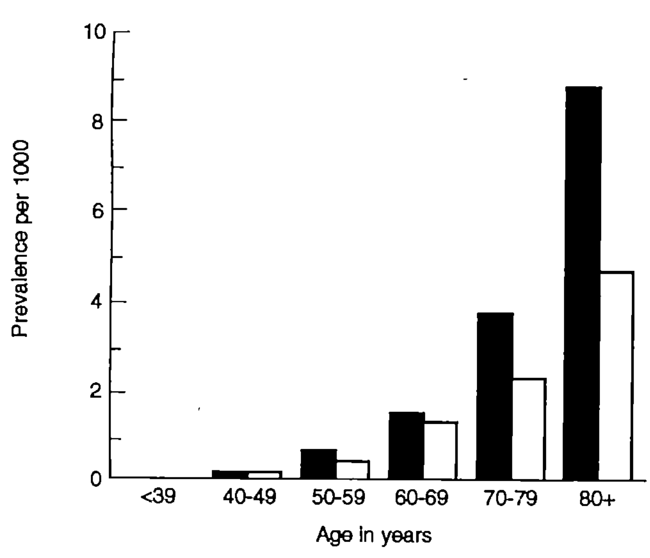

Figure 1 *Age related prevalence of all patients with a venous abnormality (■) and for patients with a venous abnormality only (□) as a cause for ulceration*

Table 2 *Aetiological factors in 163 limbs with venous abnormality and chronic ulceration*

Aetiological factors	Number
Venous	104
Venous and diabetic	9
Venous and rheumatoid	11
Venous, diabetic and rheumatoid	2
Venous and arterial	24
Venous, arterial and diabetic	4
Venous, arterial and rheumatoid	6
Venous, arterial, diabetic and rheumatoid	2
Venous and essential thrombocythemia	1

Zone	Number
1	3
2	137
3	13
1+2	5
2+3	5

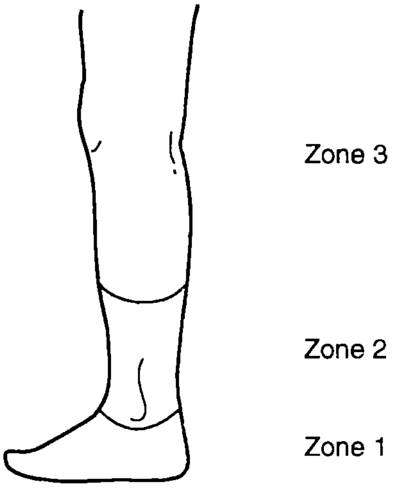

Figure 2 *Site of ulceration*

Additional aetiological factors

An abnormal venous refilling time was the only abnormality demonstrated in 104 of the 163 limbs (64 per cent). Additional aetiological factors were found in the other 59 limbs (36 per cent) (*Figure 1* and *Table 2*). Arterial ischaemia was found in 36 limbs (22 per cent), while 14 patients with 19 ulcerated limbs (12 per cent) had rheumatoid arthritis, and 15 patients with 17 ulcerated limbs (10 per cent) had diabetes mellitus.

Significant arterial ischaemia was present in only two of 40 patients (5 per cent) under 70 years of age, whereas it was found in 30 of 98 patients (31 per cent) who were over 70 This difference was significant ($\chi^2 = 8{\cdot}50$, $P < 0{\cdot}01$). The presence of any other aetiological factor plus venous disease was also significantly less common in patients under 70 years (18 per cent) compared with those over 70 (45 per cent) ($\chi^2 = 8{\cdot}01$, $P < 0{\cdot}01$).

Side of ulceration

Of the 163 limbs with chronic venous ulcers, 71 were ulcerated on the right side and 92 on the left In 25 patients the ulcers were bilateral

Site of ulceration

Ulceration was present in the gaiter area (Zone 2) in 147 limbs (90 per cent) (*Figure 2*). Ulceration was also present in Zone 1 in five of these limbs, and in Zone 3 in a further five limbs. Isolated ulceration occurred in Zone 1 (on the dorsum of the foot) in three limbs, and in Zone 3 in 13 limbs.

Chronicity of ulceration

The median duration of current ulceration was 26 weeks (range 4 weeks to 30 years). In 46 per cent of limbs the duration of ulceration was longer than 26 weeks, and in 15 per cent it was longer than 2 years (*Figure 3*). The longest time an ulcer had remained unhealed during any episode of ulceration exceeded 26 weeks in 60 per cent of patients, and 2 years in 23 per cent.

Ulceration of the legs had been occurring for more than 5 years in 47 per cent of patients, and this duration of ulcer diathesis was over 10 years in 34 per cent (*Figure 4a*). Although 24 per cent of patients were suffering their first episode of ulceration, recurrence had developed in the other 76 per cent, with more than ten episodes of ulceration in 28 per cent (*Figure 4b*).

Past history of venous thrombosis

A history of deep venous thrombosis was present for 23 patients (17 per cent). Of these patients, three had a history of pulmonary embolus and four had sustained a limb bone fracture. A history of major injury to the limb was given by 35 other patients (25 per cent); 33 suffered a limb bone fracture, one sustained a chain saw laceration and another a crush injury with amputation of the oppostie leg. Of the remaining 80 patients, 74 had undergone general anaesthesia or had had a pregnancy of 26 weeks or more on at least one occasion. Only six patients (4 per cent) had no evidence of a predisposing factor for deep venous thrombosis.

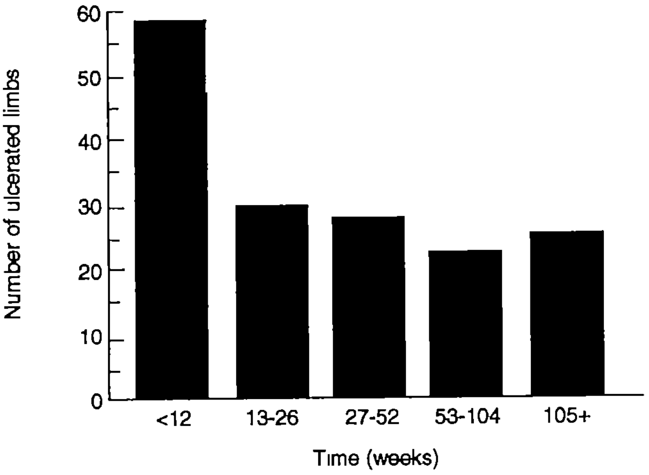

Figure 3 *Duration of current ulceration*

Previous venous surgery

A primary procedure for varicose veins had previously been carried out on 41 patients (30 per cent); in 29 patients the long saphenous vein had been stripped and in 12 the communicating veins had been divided (the only procedure in four) Individual ligation of varicosities was performed in two patients, with sclerotherapy in six others One patient underwent thrombectomy of the iliofemoral vein

Treatment dressings

Local dressings were used for 121 patients, and compression bandages for 31. In 30 patients elevation of the leg had been recommended. Of 103 patients suffering more than one episode of ulceration, 39 had been prescribed stockings for prophylaxis Twelve wore them regularly, ten occasionally and 17 patients never wore them.

Patient mobility

The mobility of patients was unrestricted (Grade 1) in 47 per cent, with a further 20 per cent mobile beyond the home (Grade 2); 33 per cent of patients were housebound, of whom 10 per cent required a walking aid (Grade 4). Another 5 per cent were chairbound (Grade 5).

Discussion

Detailed information about patients with chronic venous ulceration has not been provided by previous population based studies of leg ulcers, although prevalence could be derived from the studies conducted in the United Kingdom by Callam *et al.*[3,4] and Cornwall *et al*[5]. These authors described the characteristics of all ulcers together and did not attempt to examine venous ulcers alone. In this study we have reported only patients with a venous component to their ulceration.

An Australian population of 238 000 were screened for chronic ulceration of the leg, and to avoid sampling error in the collection of data from patients with leg ulcers, an attempt was made to assess fully all patients reported to the study. It was possible to assess 93 per cent. This differs from Callam *et al*[4] who sampled 41 per cent (600 of 1477) and Cornwall *et al.*[5] who sampled 31 per cent (100 of 327).

Prevalence data from such a study is almost certainly an underestimation of the true prevalence in the general population. This is because all cases with ulceration are not reported and all reported cases are not fully assessed. The prevalence of venous ulcer derived from the studies by Callam *et al.*[3,4] and Cornwall *et al.*[5] is higher than that of the present study, even though a similar methodology was used in all three

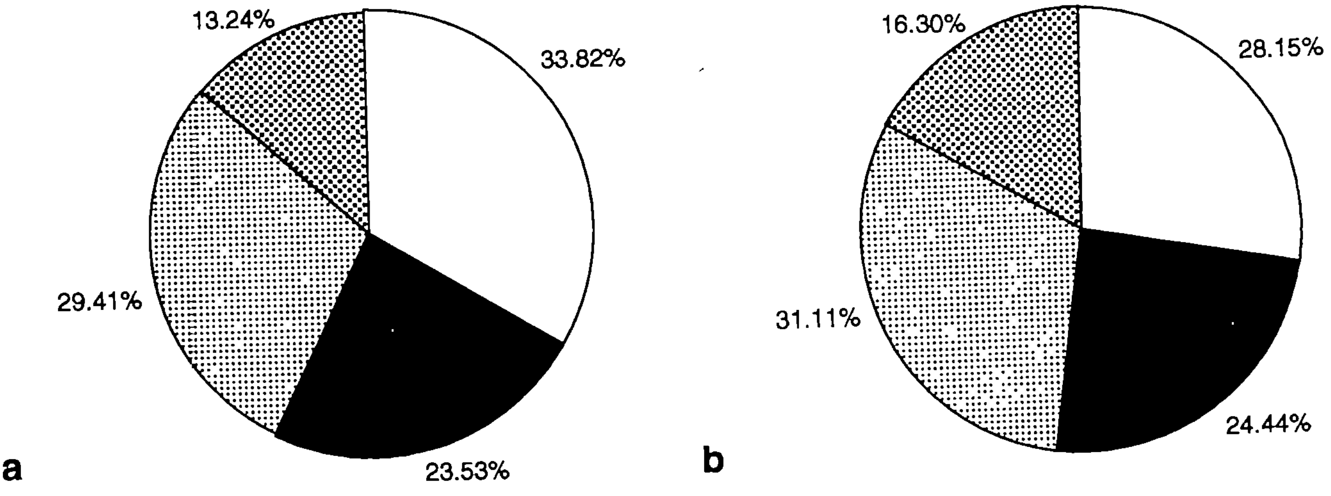

Figure 4 **a** *Duration of ulcer diathesis* ■, *1 year,* ░, *2–5 years,* ▒, *6–10 years,* □, *>10 years* **b** *Number of episodes of ulceration per patient* ■, *1 episode,* ░, *2–3 episodes,* ▒, *4–10 episodes,* □, *>10 episodes*

studies. The differences between Australian and British communities are probably less than is suggested by a comparison of the overall prevalence figures. The proportion of the study population that is elderly has considerable influence on this figure, due to the increasing prevalence of leg ulcer with age. In the present study 12·4 per cent of the study population was over 65 years old, whereas 16·3 per cent of the health district examined by Cornwall *et al.*[5] was over 65 years. Comparisons between studies can be facilitated by reporting prevalence for the subset of population at particular risk of leg ulceration (in the present case 3·3 per 1000 population for those over 60 years old). Furthermore, this study deals with chronic leg ulcers present for a month or longer, whereas Cornwall *et al*[5] screened for all leg ulcers and Callam *et al.*[3] appear to have done the same.

An abnormal refilling time on photoplethysmography was the criterion used to identify venous disease. Photoplethysmography has advantages over other laboratory methods in that it is portable, non-invasive, and can be used in patients with restricted mobility; 10 per cent of our patients used a walking aid and 5 per cent were chairbound. Only 57 per cent of limbs with chronic ulcers in this study had a venous abnormality. This is considerably less than the 76 per cent reported by Callam *et al.*[4], who made a clinical assessment of the presence of venous disease. Cornwall *et al.*[5] used photoplethysmography, and found venous disease in 81 per cent of limbs studied. However, patients with isolated ulceration of the foot were excluded from that study. In the present study, when patients with ulceration confined to Zone 1 (the foot) were excluded from analysis, venous disease was noted in 67 per cent of limbs. This remains considerably less than was found by Cornwall *et al.*[5], and may indicate that a real difference does exist in the prevalence of chronic venous ulcer between Australia and the United Kingdom.

Although more patients with chronic venous ulcer were women, the prevalence of chronic venous ulcer was not significantly different between men and women at any age. The apparent difference reflected the increased prevalence of venous ulcer among the elderly, who are mostly women.

A past history of venous thrombosis in only 17 per cent of patients is in keeping with reviews of outpatient records[9]. However, we found that another 79 per cent of patients had a predisposing factor to deep venous thrombosis (major leg injury[10,11], general anaesthesia[12], or pregnancy[13]). This supports the view that many patients with venous ulcer have previously had a subclinical deep venous thrombosis[8]. The present study showed that venous ulcer is more common on the left leg, which is consistent with the increased frequency of deep venous thrombosis on the left[14].

Each of the indices of chronicity of ulceration underscores the persistence of the condition. However, the observation that only 22 per cent of patients were treated with compression bandaging and that only 12 per cent with more than one episode of ulceration wore elastic stockings regularly indicates that more can be done to improve the management of venous ulceration in this Australian community.

Arterial disease was present in 22 per cent of limbs with a venous disorder. This is of particular importance since the methods of treatment of venous ulcers and ischaemic ulcers are very different, and the treatment of mixed ulcers depends on which is the major abnormality. There are, however, no analytical grounds for determining which abnormality is the dominant influence on wound healing.

The definition of a chronic leg ulcer as a lesion that has failed to heal after 1 month is arbitrary, but embodies the notion of delayed healing. The definition of a chronic venous ulcer used in this study was the presence of a venous abnormality in a limb with a chronic ulcer. This enabled the scope of ulceration due to venous disease in the community to be assessed. Browse *et al.*[8] define a venous ulcer as a lesion 'caused by an abnormality of the veins draining the limb', and it is worthy of note that at least one other aetiological factor was present in 36 per cent of limbs reported in the present study. How much each factor contributes to delay in healing is unknown and so it is important to consider other concurrent aetiological factors for ulcer when assessing studies of venous ulcer treatment.

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Influence of phlebographic abnormalities on the natural history of venous ulceration

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Eighty-five limbs in 73 patients with a healed venous ulcer were assessed by ascending and descending phlebography, foot volume plethysmography and transcutaneous oxygen measurements. Forty-four limbs had post-thrombotic changes on ascending phlebography. In 24 (28 per cent) these extended into the femoral vein, while in 20 (24 per cent) only the calf veins were involved. In the 41 limbs (48 per cent) with normal deep veins on ascending phlebography, 11 had evidence of localized incompetence of the calf communicating veins, 14 had either long saphenous incompetence, deep vein reflux to the level of the knee or below, or both of these abnormalities, and 16 limbs had no phlebographic abnormalities. However all limbs had a decreased half volume refilling time on foot volume plethysmography. Limbs with post-thrombotic changes extending into the femoral vein were associated with a significantly longer history of ulceration and more ulcer recurrences than limbs with calf vein damage ($P<0{\cdot}05$ *for each) and limbs with normal deep veins* ($P<0{\cdot}01$ *for each). However, these limbs did not have lower transcutaneous oxygen ratios or longer times to achieve ulcer healing. Ascending phlebography identified a group of limbs with extensive post-thrombotic changes in which there was a higher incidence of ulcer breakdown, but this was not associated with a delay in ulcer healing.*

Ascending phlebography has been used to assess limbs with venous ulcers since Bauer's work on the importance of post-thrombotic ulceration[1]. The incidence of post-thrombotic changes and incompetent lower leg communicating veins in limbs with venous ulceration has been demonstrated in many studies[1–4]. The influence of the presence and extent of post-thrombotic damage judged by phlebography on the natural history of venous ulceration as far as we can ascertain has never been assessed.

Limbs with phlebographic evidence of post-thrombotic damage have been shown to have a much higher incidence of recurrent ulceration than limbs with normal deep veins after surgical ligation of the incompetent communicating veins[4]. It might therefore be expected that the more extensive the post-thrombotic changes, the more severe would be the ulcer diathesis

A number of different methods have been used to assess the functional abnormality in limbs with venous ulceration. These include foot vein pressure measurements[5,6], assessment of the deep and superficial veins by hand-held Doppler ultrasound[7], and a variety of plethysmographic techniques using air[8], light reflection[9], water[10], and strain gauges[11] These methods of assessing calf pump function do not always correlate with the presence of phlebographic abnormalities, but may represent a more accurate method of determining minor malfunction of the calf pump mechanism.

Skin hypoxia is considered to be one possible factor in the development of venous ulceration[12], and has been shown by the transcutaneous oxygen measurements are lower in limbs with venous ulceration[13–15]. The relationship between the venous abnormality, assessed by ascending phlebography, and the degree of skin hypoxia has not been previously determined.

The aim of this study was to show whether abnormalities found on ascending and descending phlebography related to the natural history of ulceration, to the calf pump function as assessed by foot volume plethysmography, and to the transcutaneous oxygen levels of the ulcer bearing skin

Patients and methods

Investigations were performed to exclude an alternative cause of the ulceration on completion of healing. These consisted of a random blood glucose, the Rose Waaler titre, a rheumatoid factor latex fixation test, the antinuclear antibody titre and the arterial Doppler ankle/brachial pressure index In the absence of an alternative pathology the diagnosis of venous ulcer was accepted if an abnormal half volume refilling time was shown by foot volume plethysmography This was performed using a modification[16] of the technique described by Norgren[10]. The half volume refilling time, TV$_{1/2}$, which is a measure of venous reflux, and the relative expelled volume, EV$_{rel}$ (expelled volume divided by the volume of the foot), which is a measure of the pumping function of the calf muscle, were calculated. The normal ranges for these measurements in this department are 15–35 s and 1·0–2·0 ml/100 ml respectively[16].

At entry into the study, the history of ulceration was recorded for each affected limb This included the time of onset of the first ulcer, the longest time taken for an ulcer to heal, and the number of recurrences since the first ulcer. Details of past surgery for varicose veins and incompetent lower leg communicating veins, and a past history of deep vein thrombosis or pulmonary embolism were also recorded.

Ascending and descending phlebography were performed on all limbs with healed ulcers. Ascending phlebography was done using a standard technique[17]. With the patient in the semierect position 50–100 ml iopamidol 300 was injected into a vein on the dorsum of the foot with tourniquets applied from the ankle. A series of films using a fluoroscope were taken of the calf veins, the femoral veins, and the iliac veins. The criteria used to diagnose post-thrombotic damage on the ascending phlebogram were: an absence of venous channels, abnormal collateral veins bypassing areas of obstruction, reduplicated or irregular venous lumina, absence or distortion of venous valves. Incompetent lower leg communicating veins were diagnosed by the presence of dilated valveless channels through which contrast passed from the deep to the superficial veins

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Limbs with post-thrombotic changes were classified into two groups, those with changes confined to the calf, and those with more extensive changes involving the superficial femoral vein. This latter group also included limbs with abnormalities extending as far as the inferior vena cava. The limbs with post-thrombotic damage involving the superficial femoral veins were further subdivided into limbs with occluded segments and limbs with recanalization of a patent main channel.

Descending phlebography was performed using the techniques of Lea Thomas *et al.*[18] The examinations were carried out in the supine position. The common femoral vein was cannulated and the patient was asked to perform a sustained Valsalva manoeuvre during which a bolus of 20 ml of iopamidol 300 was injected. This bolus of contrast was given after the patient had maintained a pressure of 40 mmHg for at least 12 s by blowing into the barrel of a 10 ml syringe attached to a sphygmomanometer Films were taken from the groin The passage of contrast down to or below the level of the knee was considered to be abnormal[19] Long saphenous incompetence was diagnosed on descending phlebography when contrast was observed to reflux down a dilated long saphenous vein[20].

The tissue oxygen measurements were obtained from a transcutaneous oxygen monitor TCM-2 (Radiometer, Copenhagen), with the electrode heated to 45°C. The patient lay supine and measurements were taken from an electrode placed on the leg 7 5 cm above the medial malleolus, and from another electrode placed on the anterior aspect of the upper arm, which was used as a reference site. The results have been expressed as a ratio of the reading from the leg over the reading from the arm The range of this ratio for a group of normal subjects of similar age and sex has previously been established in this department as 0·91–1·11 (Reference 21)

Statistical analysis was done using the χ^2 test for ulcer history, the log rank test for ulcer healing, and the Wilcoxon rank sum test for the results of phlebography, transcutaneous oxygen measurements, and foot volume plethysmographic measurements.

Results

Eighty-five limbs in 73 patients were entered into the study. There were 40 women, three with bilateral ulceration, and 33 men, nine with bilateral ulceration. The median age was 63 years, with a range from 24 years to 88 years. All patients had an abnormal half volume refilling time on foot volume plethysmography, and a Doppler arterial ankle/brachial pressure index greater than 0·9.

Ascending phlebography

Forty four (52 per cent) of the 85 limbs had post-thrombotic changes on the ascending phlebogram. In 24 limbs (28 per cent) the post-thrombotic changes extended into the superficial femoral vein or more proximally. In eight limbs (9 per cent) these changes extended to involve the iliac veins, and in one limb they were limited to the iliac segment. Fourteen of the 24 limbs with femoral vein involvement had occluded segments, and these occlusions extended into the iliac veins in six limbs. Twelve of these 24 limbs had an associated incompetence of the calf communicating veins. In 20 limbs (24 per cent) the post-thrombotic changes were confined to the calf and 14 of these limbs had incompetent calf communicating veins. Eleven limbs with normal deep veins (13 per cent) had localized incompetence of the calf communicating veins.

Descending phlebography

A descending phlebogram could not be performed in eight limbs with extensive post-thrombotic changes because the femoral vein was occluded There was reflux of contrast to knee level or below in seven of the 16 limbs examined in which post-thrombotic changes extended above the calf, and in six of the 20 limbs in which post-thrombotic changes were confined to the calf. Ten limbs with normal deep veins had long saphenous incompetence, but no deep vein reflux. Four limbs with normal ascending phlebograms had femoral vein reflux to the knee level or below on descending phlebography.

Normal phlebography

Sixteen limbs had no abnormality on either ascending or descending phlebography.

Ulcer history

The ulcer history was considered separately for the three groups of limbs: those with normal deep veins, those with post-thrombotic changes confined to the calf, and those with post-thrombotic changes extending to the superficial femoral vein or above. *Table 1* shows that ulceration had been present for significantly longer in limbs with extensive post-thrombotic changes than in limbs with post-thrombotic changes confined to the calf ($\chi^2 = 7{\cdot}142$, $P < 0{\cdot}05$) or in limbs with normal deep veins ($\chi^2 = 12{\cdot}903$, $P < 0{\cdot}01$). There was no significant difference in the duration of ulcer history between limbs with normal deep veins and those with post-thrombotic changes confined to the calf ($\chi^2 = 2{\cdot}225$, $P > 0{\cdot}10$).

Table 2 shows that limbs with extensive post-thrombotic changes had a significantly longer period with an unhealed ulcer than limbs with normal deep veins ($\chi^2 = 10{\cdot}153$, $P < 0{\cdot}01$). Limbs with post-thrombotic changes confined to the calf fell between these two extremes and did not differ significantly from either.

Table 3 shows that there were more episodes of ulceration in limbs with extensive post-thrombotic changes than in the limbs with normal deep veins ($\chi^2 = 13{\cdot}817$, $P < 0{\cdot}01$) or in limbs in which the post-thrombotic changes were confined to the calf ($\chi^2 = 6{\cdot}635$, $P < 0{\cdot}05$). There was, however, no difference between the number of recurrences developing in limbs with normal deep veins and limbs with post-thrombotic changes confined to the calf.

Transcutaneous oxygen measurements

The transcutaneous oxygen ratios were similar in all three groups of limbs with no significant differences demonstrated by

Table 1 *Number of limbs according to duration of ulcer history and state of deep veins on ascending phlebography*

	Duration of history			
	<1 year	1–5 years	>5 years	Overall number
Normal deep veins	13	16	12	41
P-T calf	8	4	8	20
P-T extensive	2	4	18	24

P-T, post-thrombotic changes

Table 2 *Number of limbs according to longest duration of an unhealed ulcer and state of deep veins on ascending phlebography*

	Longest duration of unhealed ulcer			
	<6 months	6–12 months	>1 year	Overall number
Normal deep veins	23	8	10	41
P-T calf	7	6	7	20
P-T extensive	5	4	15	24

P-T, post-thrombotic changes

Table 3 *Number of limbs according to ulcer recurrence and state of deep veins on ascending phlebography*

	Ulcer recurrence			
	First ulcer	1–2 recurrences	3 or more recurrences	Overall number
Normal deep veins	21	14	6	41
P-T calf	11	5	4	20
P-T extensive	7	3	14	24

P-T, post-thrombotic changes

Table 4 *Foot volume plethysmography results according to the state of the deep veins*

	EV_{rel} (ml/100 ml)		$TV_{1/2}$ (s)	
	No tourniquet	AK tourniquet	No tourniquet	AK tourniquet
Normal deep veins	0·86* (0·09–2·20)	0·99* (0·29–2·13)	3·00† (0·00–13·50)	6·75† (1·00–37·50)
P-T calf	0·92 (0·13–2·13)	1·17 (0·00–3·38)	4·50* (1·50–10·50)	8·25 (1·50–40·50)
P-T extensive	0·72 (0·10–1·59)	0·80 (0·14–2·52)	2·25* (0·00–9·00)	2·25 (0·00–5·25)

Values are median(range) * $P<0{\cdot}01$ Wilcoxon rank sum test; † $P<0{\cdot}03$ Wilcoxon rank sum test; EV_{rel}, relative expelled volume; $TV_{1/2}$, half volume refilling time; P-T, post-thrombotic changes; AK tourniquet, above knee tourniquet

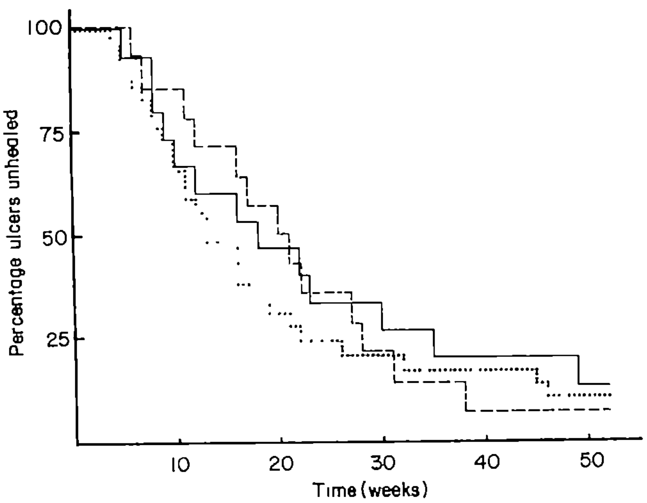

Figure 1 *Time to total healing of ulcerated limbs separated according to state of the deep veins on ascending phlebography. P-T, post-thrombotic changes, ——, P-T changes above calf (15); – – –, P-T changes calf (14), ·····, normal deep veins (29)*

Wilcoxon rank sum tests. The median ratio for normal limbs was 0·71, for limbs with post-thrombotic changes confined to the calf 0·66, and for limbs with extensive post-thrombotic changes 0·77.

Foot volume plethysmography

Table 4 shows that there was no significant differences in the EV_{rel} between any of the three groups of limbs when the tests were performed without a tourniquet. There was a significantly shorter $TV_{1/2}$ for limbs with extensive post-thrombotic changes than for limbs with post-thrombotic changes confined to the calf (2·25 s versus 4·50 s, $P<0{\cdot}01$). However, there was no significant difference in the $TV_{1/2}$ between limbs with normal deep veins and limbs with post-thrombotic changes confined to the calf, or limbs with extensive post-thrombotic changes.

The application of an above knee tourniquet significantly improved the EV_{rel} and $TV_{1/2}$ in limbs with normal deep veins ($P<0{\cdot}01$, and $P<0{\cdot}03$) but did not significantly alter these measurements in limbs with extensive post-thrombotic changes. When the EV_{rel} and $TV_{1/2}$ were compared in limbs with occluded deep veins and those with recanalized deep veins, no significant differences were apparent.

Past history of deep vein thrombosis

Nineteen patients with 21 previously ulcerated limbs gave a history of past deep vein thrombosis, and two patients with unilateral ulceration gave a history of previous pulmonary embolism. In ten patients with 12 ulcerated limbs the clinical diagnosis of deep vein thrombosis had been confirmed by phlebography, and in nine patients with unilateral ulceration the diagnosis of a deep vein thrombosis depended on clinical history and examination alone. The two patients with previous pulmonary embolism had had this confirmed by ventilation perfusion lung scan.

Patients gave a history of either deep vein thrombosis or pulmonary embolism associated with 16 of the 24 limbs with post-thrombotic changes extending into the femoral vein. For all the other ulcerated limbs the clinical incidence of deep vein thrombosis and pulmonary embolism was much lower; for limbs with post-thrombotic changes confined to the calf it was 3 out of 20 (15 per cent); for limbs with incompetent communicating veins only it was two out of 11 (18 per cent) and limbs with normal deep veins it was two out of 30 (7 per cent).

Previous treatment of varicose veins

Twenty-four of the 85 limbs included in this study had either had surgery to the superficial veins[19] or had been treated by sclerotherapy[5]. In three limbs both subfascial ligation of the communicating veins and long saphenous surgery had been carried out, and in one limb only subfascial ligation of the incompetent calf communicating veins had been performed, these four limbs all had evidence of post-thrombotic changes on phlebography, and all four still had phlebographic evidence of incompetent lower leg communicating veins when re-examined by ascending phlebography. Only one of the 18 limbs that had had previous long saphenous surgery had evidence of long saphenous incompetence on descending phlebography. Four of the 16 limbs with no abnormality on either ascending or descending phlebography had had surgery in the past to the long saphenous vein and one had had sclerotherapy to calf varicosities. The remaining 11 limbs with normal phlebograms had clinical varicose veins.

Rate of ulcer healing

Fifty-one of the 73 patients (58 limbs) were serially enrolled in a study of venous ulcer healing using a standard dressing regimen of Calaband® paste bandage (Seton, Oldham, UK) covered by two Elastocrepe® bandages and Tubigrip® stockingette (Seton). There was no significant difference in initial ulcer size when the limbs were separated into the three groups determined by ascending phlebography. There was also no significant difference in healing rate between the three groups ($P=0{\cdot}73$, log rank statistic $=0{\cdot}637$, *Figure 1*).

Discussion

This study confirms the clinical impression that limbs with extensive post-thrombotic changes have a significantly longer history of ulceration, and significantly more ulcer recurrences.

The group of limbs with extensive post-thrombotic damage could not be differentiated from the other limbs by the measurement of transcutaneous oxygen in the ulcer bearing area. Nor was there any evidence that ulcer healing was delayed in these post-thrombotic limbs. These findings imply that a venous ulcer represents the end stage of a disease process, which is irrespective of the functional abnormality of the leg. Local factors involved in the process of wound healing, rather than the extent of the venous damage, appear to be of more importance in determining the rate at which ulcers heal.

Limbs with extensive post-thrombotic changes had a significantly greater degree of deep vein reflux shown by a decreased refilling time on foot volume plethysmography. This abnormality of calf pump function was associated with a more severe ulcer diathesis. However, the transcutaneous oxygen measurements did not identify patients liable to develop recurrent ulceration

In the 16 limbs with abnormal calf pump function in which phlebography demonstrated normal deep veins and no incompetence of the saphenous, femoral or communicating veins, the exact nature of the venous abnormality remains uncertain. Incompetent communicating veins may have been present in some of these limbs although these were not demonstrated by phlebography[17]. It is also possible that some limbs had functional abnormalities of the calf muscle pump which phlebography could not detect.

There was no evidence of an increase in foot volume on exercise in limbs with phlebographic occlusion of the superficial femoral or iliac veins. It would therefore appear that an occlusion of these veins does not result in a functional obstruction to venous return. This is presumably because, although the major veins are occluded, there are sufficient collaterals to avoid impedance to blood flow. These collaterals do not contain competent valves and therefore result in rapid venous refilling.

We have demonstrated that phlebography can readily identify those limbs at risk of recurrent ulceration. These limbs with severe post-thrombotic damage are often refractory to eradication of incompetent superficial and communicating veins[4]. The successful prevention of recurrent ulceration in such high risk limbs demands regular wearing of support hosiery, combined perhaps with fibrinolytic enhancement and possibly one of the direct surgical methods of improving valve function of the deep veins[22–25].

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Early computed colour echo Doppler imaging following renal transplantation

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Thirty patients with renal allografts were monitored for 15 postoperative days by colour-coded Doppler imaging and categorized as stable, rejection, acute tubular necrosis and cyclosporine toxicity. All forms of graft dysfunction showed significantly raised resistance (P < 0·01) *and pulsatility* (P < 0·01) *indices (RI and PI, respectively). It was not possible to use Doppler imaging to differentiate the cause of graft dysfunction, but stable grafts in patients with high cyclosporine levels had significantly higher RI* (P < 0·04) *and PI* (P < 0·04) *than similar grafts in patients with cyclosporine levels in the therapeutic range.*

Ultrasonic Doppler imaging of renal blood flow is proposed as a suitable method for detecting and differentiating transplant dysfunction[1–6]. Earlier investigations were limited in scope and accuracy by real-time grey scale Doppler systems. The recent advent of colour-coded Doppler imaging allows examination of the intrarenal vasculature[5–7], which may reflect the true state of renovascular resistance. This study examines the ability of colour-coded Doppler imaging to detect and differentiate different types of renal transplant dysfunction.

Colour Doppler imaging of the renal graft was carried out repeatedly over the first 15 days after transplantation. Rejection episodes were documented by the use of renal biopsies and fine needle aspiration cytology (FNAC). Regular plasma cyclosporine estimations have enabled a correlation of the recorded resistive and pulsatility indices (RI and PI, respectively) using Doppler waveform analysis, with an accurate documentation of graft status.

Patients and methods

The study group comprised 30 patients who underwent renal transplantation between February and July 1990. The age range was 16–63 years, with a mean of 38·4 years and male:female ratio of 2:1. The study period was confined to the first 15 postoperative days, and patients were monitored daily by measurement of serum urea, creatinine, electrolytes and 24-h urine output. Plasma cyclosporine levels were estimated every third day using the Abbotts TDX® system (Abbott Laboratories Ltd, Maidenhead, UK) by a fluorescent competition technique using polyclonal antisera. Cyclosporine was administered initially in a dose of 15 mg/kg per day and adjusted to reduce plasma cyclosporine levels to < 1000 ng/ml. Patients with preformed antibodies and those with rejection failing to resolve with three pulses of 0·5 g intravenous methylprednisolone were treated with cyclosporine 6–10 mg/kg per day, prednisolone 0 3 mg/kg per day, and azathioprine 1 mg/kg per day.

The graft cellular infiltrate was monitored by FNAC using the technique described by Hayry and von Willebrand[8]. FNACs were performed on the same day as Doppler imaging where possible or, more frequently, when the patient exhibited clinical signs of rejection. Alternatively, diagnosed rejection episodes were specifically documented by a biopsy from the upper end of the graft using an 18-gauge Biopty® system (Radioplast AB, Uppsala, Sweden) under ultrasound guidance.

In all, 112 Doppler studies were performed using an ACUSON 128 computed colour-coded Doppler scanner with a 3·5 MHz range gated pulsed Doppler sector transducer (ACUSON Corporation, California, USA). Real-time sector images showing blood flow in coloured patterns were used to guide the cursor to the vessel to be sampled.

The main renal artery (MRA), interlobar arteries (IL) and arcuate vessels (ARC) were visualized, and cursors placed appropriately to obtain Doppler signals. The angle and the gate of the Doppler beam were adjusted to suit the direction of the blood flow in the vessels. Built-in software was used for Doppler waveform analysis to derive the RI and PI. This involved manual marking of the points of maximum and minimum frequency shift on the frozen image of the waveforms on screen. The indices were then calculated by the in-house software over three waveforms for each vessel and averaged.

Seventy-four FNAC examinations and 40 needle biopsies were performed in the 30 patients. By study of the clinical, laboratory and histopathological data a daily status of the graft was derived: *stable function* was defined as normal or normalizing graft function, *rejection* was poor or deteriorating graft function in the presence of a total corrected increment (TCI) of greater than 2·5 or a renal biopsy demonstrating tubulointerstitial lymphocyte infiltration and/or vascular rejection, *acute tubular necrosis* (*ATN*) was poor or no graft function from day 1 without evidence for graft rejection on FNAC or biopsy; *cyclosporine nephrotoxicity* was defined as deteriorating graft function with plasma cyclosporine levels > 1000 ng/ml, with improvement in renal function following a reduction in cyclosporine dosage.

It was then possible to allocate Doppler indices retrospectively to the status of the graft and examine their significance. Statistical analyses were performed using the Mann–Whitney *U*-test for non-parametric data. For multiple comparisons between the groups, the data were re-tested with a non-parametric one-way analysis of variance using a χ^2 approximation to the distribution of the Kruskall–Wallis test statistic.

Results

Of the 30 patients undergoing transplantation, rejection was diagnosed in 22 and successfully treated in all but one. Eight patients had delayed graft function attributed to ATN and four of these patients were documented as developing graft rejection prior to recovery from the ATN. Six patients had cyclosporine nephrotoxicity and eight patients were found to have high cyclosporine levels in association with biopsy-proven rejection.

The RI and PI (median and interquartile ranges) from the Doppler studies on the MRA, IL and ARC vessels are shown in *Table 1* and can be compared with results obtained from examinations performed during the three major tyes of graft dysfunction. There was a slight fall in the indices passing peripherally from the MRA to the ARC vessels. There were significant increases in all of the indices with all forms of graft dysfunction and this was most marked in changes in the PI. Comparisons of the three different types of graft dysfunction did not show a significant difference in either RI or PI obtained from any of the vessel sites. Although the indices were increased in grafts showing dysfunction there was no discriminatory power in the Doppler indices.

An analysis of patients with elevated cyclosporine levels but with stable graft function showed that the stable grafts with cyclosporine levels > 1000 ng/ml had elevated indices in all three vessels when compared to stable grafts with cyclosporine levels < 1000 ng/ml; however, this was only statistically significant for the main renal artery (*Table 2*).

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Table 1 *Resistive and pulsatility indices (median and interquartile range)* versus *graft status*

Status	Index	MRA	IL	ARC
Stable (*n*=33)	RI	0·67+0·08	0·60+0·09	0·59+0·08
	PI	1·20+0·27	0·99+0·30	0·91+0·23
Rejection (*n*=31)	RI	0·75+0·12	0·69+0·15	0·66+0·08
	PI	1·55+0·78	1·26+0·50	1·14+0·38
ATN (*n*=24)	RI	0·76+0·16	0·74+0·14	0·67+0·11
	PI	1·43+0·66	1·29+0·56	1·18+0·26
CYNT (*n*=8)	RI	0·73+0·08	0·65+0·13	0·64+0·13
	PI	1·44+0·28	0·98+0·44	1·17+0·33

Comparisons of indices from stable grafts with the rejecting and ATN grafts for both RI and PI gave values of $P<0·01$ in all instances. Comparison of stable graft values with the CYNT group gave $P<0·02$ for MRA RI and PI, and ARC PI, but there was no significant difference for the other vessel parameters. *n*, Number of Doppler examinations; MRA, main renal artery; IL, interlobar arteries, ARC, arcuate vessels; ATN, acute tubular necrosis; CYNT, cyclosporine nephrotoxicity

Table 2 *The effect of alterations in cyclosporine levels on the RI and PI (median and interquartile range) of stable grafts*

Cyclosporine level	Index	MRA	IL	ARC
<1000 ng/ml	RI	0·63+0·06	0·61+0·05	0·57+0·08
(*n*=11)	PI	1·10+0·27	0·94+0·21	0·87+0·17
>1000 ng/ml	RI	0·73+0·12	0·61+0·15	0·64+0·08
(n=7)	PI	1·41+0·52	0·99+0·47	1·03+0·44

$P<0·04$ was achieved for comparisons of RI and PI of the MRA. Comparisons of indices of the two groups did not reach statistical significance for the IL or ARC vessels. *n*, Number of Doppler examinations, MRA, main renal artery; IL, interlobar arteries; ARC, arcuate vessels

Discussion

After successful kidney transplantation, the renal blood flow improves steadily concomitant with an increase in the glomerular filtration rate. During rejection episodes most grafts show a fall in the calculated volume of blood flow[1]. An increase in the index of vascular impedance detected by Doppler studies (and calculated from alterations in waveform morphology), is attributed to an increase in microvascular resistance as a result of vasomotor constriction, or a mechanical effect of interstitial oedema within the renal capsule[9], demonstrated by raised intrarenal pressure with rejection[10,11].

Attempts to measure blood flow are complicated by many technical factors, but changes in the Doppler waveform morphology during graft dysfunction have been well documented[1,2,12]. These changes have been quantified, attempting indirectly to express changes in renal blood flow as a result of altered vascular impedance by the following measures: (1) renal·femoral artery ratio[1] acceleration time of the systolic component[2], (2) diastole:systole ratio[3], (3) PI; (4) Pourcelot index or RI[13,14]; (5) area under curve 1:2 ratio[15].

In this study, RI and PI were used as useful indices of Doppler waveform analysis without the problems of trying to estimate the renal blood flow.

Colour-coded Doppler imaging has recently been investigated to define its role in non-invasive monitoring of renal allograft function in the early postoperative period[16–18]. The high resolution achieved and the colour-coding facility produce a high quality record of Doppler signals from a precise location in the vascular tree. One potential source of human error is the requirement for the manual marking of the waveform image prior to RI and PI calculation by the internal computer software. This problem can probably be resolved by the use of new technology in the form of an automated waveform analysis system. In this study the average of the results from three observations for each vessel was used to reduce the chance of error.

The vascular resistance fell as the vessels were traced peripherally in the kidney, confirming that the kidney has a low-resistance vascular bed in contrast to the peripheral circulation. This finding can be deduced from the work of Rigsby *et al.*[19] and may explain the continuous antegrade flow during diastole in renal blood vessels. Graft status may be assessed by repeated FNAC, biopsy and cyclosporine assays performed at the time of Doppler studies, and these results demonstrate that the RI and PI are significantly elevated in all forms of graft dysfunction and that these changes are seen in the MRA, IL and ARC vessels.

Examination of the three vessel sites during rejection demonstrated significant elevations in the Doppler indices, and the effect of the rejection process in the MRA, IL and ARC vessels was equivalent. The indices from the MRA probably reflect the overall resistance of the renal vascular bed.

Patients with ATN showed the maximal elevations in Doppler indices, contrary to the findings of some[7,20], but consistent with others[5]. It must be presumed that the intense interstitial oedema in grafts with ATN produces changes in the renovascular resistance.

Significant changes in the Doppler waveform occur in cyclosporine nephrotoxicity[15]. The results of the present study confirm that cyclosporine can induce renal dysfunction, demonstrated by raised Doppler indices in cyclosporine nephrotoxicity and an increase in the renal vascular resistance in patients with stable graft function but high cyclosporine levels.

Attempts to differentiate rejection from ATN[5,7], and from cyclosporine nephrotoxicity[3], using Doppler as a primary mode of investigation have in the past proved unsuccessful. This problem has not been overcome using colour-coded computed Doppler imaging.

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Preoperative clinical evaluation as a predictor of cardiac complications after infrarenal aortic reconstruction

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This paper analyses cardiac risk factors in 93 consecutive patients undergoing elective infrarenal aortic reconstruction over a 2 year period During the perioperative or postoperative period, 26 patients sustained a total of 42 cardiac complications. Eight patients had myocardial infarction, 14 left ventricular failure and 15 arrhythmias. There were five cardiac-related deaths. Angina was the only statistically significant risk factor in predicting postoperative cardiac problems. A multivariate analysis identified a high-risk group of patients in whom cardiac complications after operation were common.

In recent years there has been a steady decline in deaths after elective infrarenal aortic reconstruction. Reported series over the last 10 years or so show an operative mortality rate of 3–10 per cent for non-ruptured aortic aneurysm operations[1]. Recently, a consecutive series of over a hundred elective aortic reconstructions was described with no deaths[2]. Most specialist vascular or general and vascular surgical units would expect to achieve a 30-day postoperative mortality rate of 5 per cent or less In this unit, between January 1988 and July 1990, 126 elective aortic reconstructions were performed with seven deaths (a 5·6 per cent 30-day mortality rate). On the other hand, mortality rate is unacceptably high when aortic reconstruction is performed by the 'occasional' vascular surgeon[3].

Morbidity after these operations is common but, although most patients survive respiratory or gastrointestinal problems, cardiac and renal complications are more likely to be fatal[4]. Death after aortic operation is mainly due to cardiac causes[5] Severe postoperative cardiac complications occurring in up to 15·6 per cent of cases have been reported; this is because of the high incidence of severe coronary artery disease in these patients. By contrast, cardiac complications have been found to occur in only 8 per cent of cases after other intrathoracic or intraperitoneal operations, and 1·6 per cent after transurethral prostatic resection[6].

Non-invasive tests of cardiac function attempt to relate changes in coronary artery blood flow (induced by exercise or pharmacological dilatation) with subsequent myocardial ischaemia (measured by electrocardiogram) or ventricular perfusion or movement (measured by isotope scanning). In this context, dipyridamole thallium tests are more reliable than stress electrocardiography[7]. All of these tests are potentially dangerous, time consuming and expensive, and the more reliable ones are not freely available in all hospitals. Correlation between left ventricular stroke work index and a modification of Goldman's clinical risk factor index is good[8].

This paper describes a prospective study which re-evaluates clinical cardiac assessment before operation as a predictor of cardiac problems after operation.

Patients and methods

Between January 1988 and December 1989, 93 consecutive patients underwent infrarenal aortic reconstruction. There were 82 men and 11 women, age range 47–86 years (median 66 years). The indication for operation was aneurysmal disease in 51 (55 per cent), intermittent claudication in 35 (38 per cent) and rest pain in seven (8 per cent)

The abdominal incision was usually transverse, with vertical groin incisions if necessary. Of the patients with aortic aneurysm, 27 had straight grafts; the remaining patients had bifurcated grafts. The distal anastomosis was to the common or profunda femoris artery in all cases. A soft woven Dacron® (E I du Pont de Nemours, Wilmington, Delaware, USA) prosthesis was used There were 11 combined arterial reconstructions, which included grafts to the internal iliac artery (one) and popliteal artery (ten).

The preoperative cardiac risk factors analysed are listed in *Table 1* with the scoring system used, based on Detsky's modification of Goldman's risk factor analysis[9,10]. Postoperative cardiac events were recorded and a statistical analysis was performed using either a χ^2 test, with Yates' correction for continuity, or Fisher's exact test as appropriate

Results

Table 2 shows the number of patients having each of the risk factors analysed. No patient had aortic stenosis, an infarct within 6 months or left ventricular failure within 1 month before operation. None fell into the defined category of poor general medical condition. A total of 26 patients had 42 postoperative cardiac complicatons (*Table 3*). In 18 patients (19 per cent) the complications were potentially life-threatening The likelihood of complications occurring for each risk factor studied is also shown in *Table 2*. Angina was the only risk factor that reached statistical significance.

Using the multifactorial scoring system gave the majority of the patients a score of 0–5 (*Figure 1*). Ten of these 59 patients had a postoperative cardiac complication. However, most of

Table 1 *Multifactorial scoring system*

Factor	Score
Myocardial infarction	
Within 6 months	10
More than 6 months previously	5
Angina	10–20
Left ventricular failure	
Within 1 month	10
At any time	5
Aortic stenosis	20
Arrhythmia on electrocardiogram	5
Age >70 years	5
Poor general condition*	5

* $P_{O_2} < 8$ kPa, $P_{CO_2} > 6·5$ kPa, serum potassium $< 3·0$ mmol l^{-1}, serum bicarbonate < 20 mmol l^{-1}, serum urea > 18 mmol l^{-1}, serum creatinine > 260 μmol l^{-1}, abnormal serum transaminase. signs of chronic liver disease or bedridden for non-cardiac reason The presence of hypertension and diabetes mellitus were also noted but were not included in the risk score calculation

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Table 2 *Risk factors and cardiac complications after operation*

Risk factor	Total number of patients	Number of patients with cardiac complications after operation	Statistical significance
Angina			
Yes	18	12	$P<0{\cdot}001$
No	75	14	
Myocardial infarction			
Yes	29	12	n.s
No	64	14	
Hypertension			
Yes	30	12	n.s
No	63	14	
Left ventricular failure			
Yes	7	2	n.s
No.	86	24	
Diabetes mellitus			
Yes	6	3	n s.
No	87	23	
Age >70 years			
Yes	33	12	n s.
No	60	14	

Table 3 *Cardiac complications in 26 patients*

Complication	Number
Death	5
Myocardial infarction	8
Left ventricular failure	14
Arrhythmias	15
Total	42

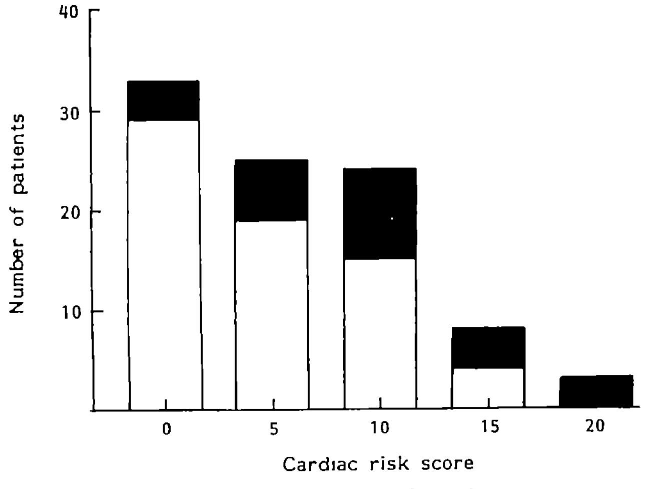

Figure 1 *Number of patients with each cardiac risk score* ■, *patients who developed postoperative cardiac complications*

the patients experiencing a postoperative cardiac complication had a score of 10–20, 16 of 34 patients with such a score had a cardiac complication ($P<0{\cdot}01$). As the score rose, the likelihood of a postoperative cardiac complication increased. Twelve per cent of patients with a zero score developed complications, whereas all three patients with a score of 20 did so. Two of the five patients who died had scores of 20 and the other three had scores of 10.

Discussion

These data show that cardiac problems are common after infrarenal aortic reconstruction, and that as the preoperative cardiac risk score rises so does the likelihood of postoperative cardiac complications. Nevertheless, 17 per cent of patients with minimal or no risk factors (score 0–5) experienced non-fatal cardiac problems after operation. Angina was the only single risk factor that reached statistical significance in this series. Although dipyridamole thallium scans may be more accurate than clinical assessment, false negative results still occur[11].

How should high risk patients be managed? Hertzer *et al.*[12] performed coronary angiography routinely on 302 patients having abdominal aortic aneurysm repair. They found 89 patients to have significant coronary artery disease suitable for bypass, which was carried out before repair of the aneurysm The mortality rate was 12 per cent, but this included two patients who died from rupture of their aneurysm between coronary artery bypass grafting and planned aneurysm surgery. Of these patients, 61 then had aneurysm repair with a 1·6 per cent mortality rate. The coronary arteries were in satisfactory condition in 167 patients, and their aneurysms were repaired without further treatment, with a 4·8 per cent mortality rate. The overall mortality rate achieved by adopting this aggressive policy was 7·8 per cent. This study was completed before coronary artery angioplasty was freely available. The operative mortality of coronary artery bypass rises with age and in the 65–70 year age group can be as high as 10 per cent[13,14] Coronary angioplasty may have a lower mortality rate, although in 674 patients aged 70 years or more the procedure-related mortality in the Milwaukee Cardiovascular Data Registry was still 7·4 per cent. This compares with an overall mortality rate of 2·4 per cent in over 8000 patients comprising their total series[15]. The other possible advantage that angioplasty might have over operation is quicker recovery, leading to a shorter interval between cardiac revascularization and subsequent aortic reconstruction.

An alternative approach is to investigate myocardial function further only if indicated on clinical grounds. Using this approach, Gouny *et al.* performed only ten coronary angiograms, and carried out only one coronary artery bypass before aneurysm repair in 261 patients[5]. In four patients, the coronary angiogram was basically normal and few patients were identified in whom cardiac revascularization seemed likely to be beneficial. The overall mortality rate of aneurysm repair in their series was 3·4 per cent.

Infrarenal aortic reconstruction can be performed relatively safely in the presence of coronary insufficiency. However, clinical evaluation is essential to ensure that any cardiac abnormality present is stable Should it not be, or if the cardiac risk score is greater than 10, alternative forms of reconstruction, such as extra-anatomic bypass for occlusive disease, should be considered. If a patient has unstable angina or left ventricular failure and a large or symptomatic aneurysm, it is appropriate to consider initial coronary angiography and revascularization. Conventional repair in high-risk patients appears to be no more dangerous than ligation and thrombosis of an aortic aneurysm combined with axillofemoral bypass. Furthermore, the latter approach has the potential disadvantage of late rupture of an inadequately thrombosed aneurysm or thrombosis of the extra-anatomic graft[16]

One caveat to this approach concerns long-term patient survival. Data from the Mayo Clinic suggest that patients over 70 years old at the time of aneurysm repair survive as long as a similar population without aneurysm[17]. However, patients under 70 years old at aneurysm repair did not survive as long as their peers, largely because of death from coronary artery disease Perhaps these younger patients are those who should be investigated routinely and have coronary artery disease corrected before aneurysm repair, provided the delay between the two procedures is not excessive.

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Effects of two methods of endothelial cell seeding on cell retention during blood flow

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The potential benefits of endothelial cell seeding depend not only on effective cell attachment, but also on the ability of the cells to resist the stresses of blood flow. We have investigated the effect of different blood flow rates on immediately seeded grafts (SHORT) *and also on preformed confluent monolayers formed by overnight incubation* (LONG). *Cells were labelled with indium and then exposed to either 100 or 200 ml/min of pulsatile blood flow. Cell retention was measured up to 120 min. At both flow rates the* LONG *seeding procedure gave significantly better cell retention than the* SHORT *method* ($P<0{\cdot}01$ *at all times*). *There was no difference in cell retention between the two flow rates in the* LONG *group, but more cells detached at the higher flow rate in the* SHORT *group* ($P<0{\cdot}01$). *We conclude that the new seeding method, using preformed confluent monolayers, significantly improves cell retention during blood flow.*

The number of vascular reconstructive procedures carried out has increased rapidly during the last two decades. Extensive research efforts have been made to produce synthetic grafts which are essentially non-thrombogenic. Endothelial cell seeding has been introduced as one such method of trying to achieve this aim We have previously shown that fibronectin significantly improves the initial attachment of endothelial cells onto polytetrafluoroethylene grafts in a static system[1]. The main test of the seeding procedure is, however, the way in which the attached cells withstand the stresses that blood flow exerts on them. Traditional seeding methods have resulted in significant cell losses after graft implantation[2], which delays the beneficial effects of seeding on graft thrombogenicity by up to 6 weeks in animal studies[3]. In an attempt to remedy this dramatic cell loss in the first few hours after implantation, we have developed a new method of seeding This entails the formation of a confluent endothelial cell monolayer on the graft before implantation. The aim of this study was to compare the cell losses in pulsatile flow using this new seeding method with those of immediate seeding procedures.

Materials and methods

Endothelial cell cultures

Endothelial cells were harvested from human umbilical veins The umbilical cord was collected within 24 h of delivery and all clamp marks and needle holes were removed. The umbilical vein was cannulated at either end and flushed with 10 ml minimum essential medium (MEM) to remove old blood. The vein was then distended with 5 ml 0·1 per cent collagenase solution (CLS I, Lorne Laboratories, Twyford, UK, calcium chloride 15 mmol/l) prewarmed to 37°C, and the whole cord was incubated for 15 min at 37°C After incubation the vein was flushed through with 20 ml MEM to remove dislodged endothelial cells, and the resulting cell suspension was centrifuged for 7 min at 200*g* and 4°C. The cell pellet was resuspended in 5 ml complete medium (medium M199, 20 per cent fetal calf serum, penicillin 100 units/ml, streptomycin 100 μg/ml, HEPES buffer 20 mmol/l, glutamine 2 mmol/l, pyruvate 1 mmol/l (all Flow Laboratories, Irvine, UK), endothelial cell growth supplement 20 μg/ml, heparin 90 μg/ml (both Sigma, Poole, UK)) and the cells were finally plated onto a 25 cm^2 tissue culture flask The cells were incubated at 37°C in 95 per cent air/5 per cent carbon dioxide for 3–7 days until they reached confluence

Labelling of endothelial cells

Once at confluence, the cells were harvested with 0·1 per cent trypsin/0·02 per cent ethylene diamine tetraacetic acid at 37°C. The trypsin was then inhibited by adding excess MEM containing 20 per cent fetal calf serum. The resulting cell suspension was centrifuged for 7 min at 200*g* and 4°C and the cell pellet resuspended in 0·5 ml serum free medium. The cells were labelled with 50 μCi indium-111 oxine (Amersham International, Amersham, UK) at room temperature for 15 min After labelling, the cells were washed three times with MEM and finally resuspended in 8 ml complete medium at a concentration of $1{\cdot}25\times10^5$ cells/ml, in readiness for seeding Labelling efficiency was determined at this point.

Cell seeding

Two seeding methods were used For both procedures a 15 cm length of polytetrafluoroethylene (PTFE) graft, a gift from W.L. Gore and Associates Incorporated (Livingstone, UK), of 4 mm internal diameter was immobilized in a seeding chamber (*Figure 1*) and sterilized. The graft luminal surface was then coated with fibronectin 20 μg/ml (Sigma) over a 1 h period.

LONG *procedure*. A syringe was used to introduce 2 ml of the labelled cell suspension into the graft via the end cannula The graft was laid horizontally in an incubator at 37°C for 20 min After this incubation period, the medium containing any unattached endothelial cells was removed The seeding chamber was then rotated 90° and a further 2 ml aliquot of fresh cell suspension was introduced into the graft lumen and incubated for 20 min. This procedure was repeated until all four 2 ml aliquots had been used and the chamber had been turned a full 360° The final aliquot was retained in the graft lumen and the seeding chamber, with graft *in situ*, incubated on a roller table, rotating at 10 rph, overnight Before inserting the graft in the perfusion circuit, the final aliquot was removed from the graft lumen.

SHORT *procedure*. This procedure also utilized the seeding chamber The labelled cell suspension was again divided into four aliquots of 2 ml Each aliquot was introduced into the graft at 5 min intervals, with 90° rotation between each. The chamber was laid horizontally between each rotation. This procedure therefore took a total of 20 min to complete Again the final aliquot was removed before the graft was exposed to blood flow The seeding efficiency was determined for each procedure.

Pulsatile flow circuit

The design of the seeding chambers made them ideally suited for insertion into a flow circuit. This allowed the seeded grafts to be studied

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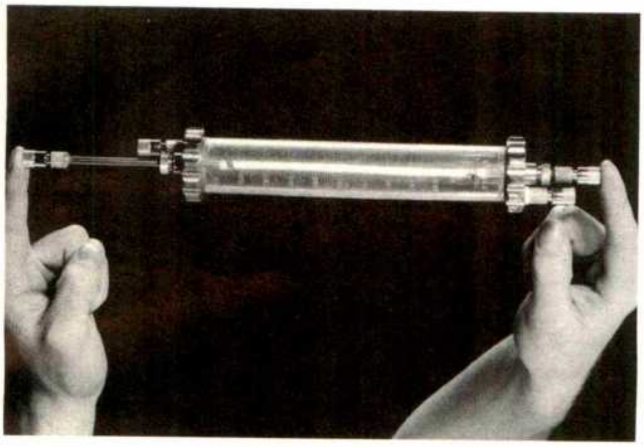

Figure 1 *Endothelial cell seeding chamber*

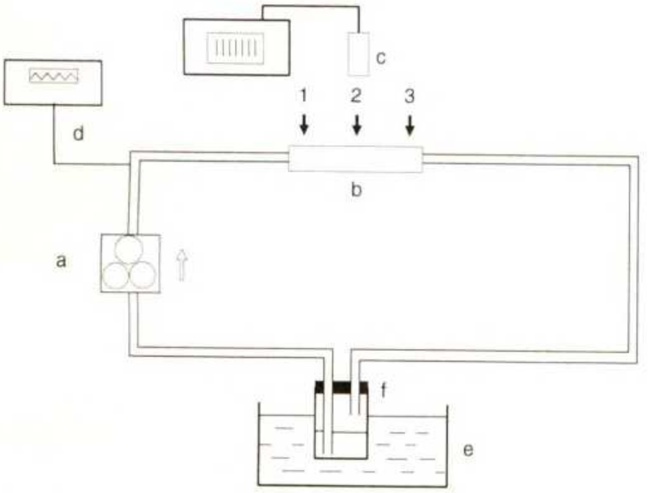

Figure 2 *Diagram of the pulsatile flow circuit: (a) pulsatile pump, (b) graft in chamber, (c) gamma counter (1,2,3, points of measurement), (d) pressure transducer, (e) water bath at 37°C, (f) blood reservoir*

without having to remove them from the chambers. The flow circuit is shown diagrammatically in *Figure 2*.

Unwanted whole human blood was obtained from the transfusion service and heparinized using 2 units heparin (Multiparin, CP Pharmaceuticals, UK) per ml blood. Seventy-five millilitres of this heparinized blood were placed in the reservoir, which was placed in a water bath at 37°C throughout the flow experiments. The reservoir consisted of a 250 ml Duran glass bottle (FSA, Loughborough, UK), the cap of which had an inlet and outlet port. The outlet port was connected on its inner aspect to a length of PTFE tubing, one end of which lay submerged below the surface of the blood. The outside aspect of the outlet port was connected to a pulsatile pump unit via a length of blood administration tubing (Travenol Laboratories Ltd., Thetford, UK). The pulsatile pump unit consisted of a pump motor (Model 7554-30), a Masterflow speed control, a pump head (7017-20) and 17 Fr gauge silicone tubing (all from CP Instruments Ltd., Bishops Stortford, UK). The pump sucked blood from the reservoir and pumped it through the graft. The set-up described allowed flow rates of between 2·8 and 280 ml/min. The blood travelled from the pump to the graft via a further length of blood administration tubing. This was connected to one of the stainless steel supporting cannulae via a luer fitting. After passing through the graft, the blood was returned to the reservoir via a third length of blood administration tubing.

Before any graft flow experiments were carried out, the pump speed control was calibrated. This was carried out by hand-timed flows using a similar circuit. The mean flow rates from a number of runs at various settings were noted and the points where the flow rates averaged either 100 or 200 ml/min were marked. In addition, to obtain some idea of the pressures exerted on the cells, a pressure transducer was inserted into the circuit proximal to the graft. This consisted of a P23XL pressure transducer, a 13 G4615-50 transducer amplifier and an 80005 thermal chart recorder (all from Gould Instruments Ltd., Hainault, UK). At a flow rate of 100 ml/min a peak pressure of 95 mmHg and a pulse pressure of the same value were obtained. The corresponding figures at 200 ml/min were again identical and measured 120 mmHg.

Calculation of cell loss

Two different flow rates were used in the experiment: 100 and 200 ml/min. These were chosen as representative of the flow rates seen in clinical practice in femoropopliteal grafts. Once the circuit had been set up, it was primed with blood by very slowly activating the pump. Only when the circuit was full with blood was the gamma activity over the graft measured using an Isotope Localization Monitor 235 fitted with a type 235 probe (D.A. Pitman Ltd., Weybridge, UK). The probe was used with the collimator set at 1 cm. Counts were recorded at three points along the graft, one at either end and one in the centre. The mean of the three counts was used in calculating cell retention. When a baseline value had been obtained, the pump was activated at the appropriate speed and left running. Further counts of gamma activity were made at the same three points along the graft at 10, 20, 30, 45, 60, 90 and 120 min. Results were expressed as percentage of initially attached cells retained at the designated time points. They were calculated using the following formula:

$$\underset{(\%)}{\text{Cells retained}} = \frac{\text{Mean counts at } x \text{ min}}{\text{Mean counts at 0 min}} \times 100$$

where x is 10, 20, 30 min, etc.

There were therefore four separate groups: SHORT at 100 and 200 ml/min and LONG at 100 and 200 ml/min. Ten replicate experiments were carried out in each group.

Qualitative examination of grafts

Each graft was prepared for qualitative assessment by both light microscopy and scanning electron microscopy. For the latter, graft segments were sectioned and placed in a glutaraldehyde (3 per cent)/paraformaldehyde (3 per cent) fixative, in 0·1 M cacodylate buffer at pH 7·2. After fixing for 2 h, the specimens were washed in 0·1 M cacodylate buffer for 1 h. Subsequently, they were added to 1 per cent osmium tetraoxide (Sigma) in 0·1 M cacodylate buffer and left for a further 1 h. The specimens were then dehydrated through graded acetone (50 per cent for 30 min, 70 per cent for 60 min, 90 per cent for 15 min and finally 100 per cent for 15 min). Further processing involved critical point drying using a Polaron E3000 critical point dryer (Bio-Rad Microscience Ltd., Hemel Hempstead, UK), and then sputter coating with gold using a Polaron E5150 coater (Bio-Rad). The specimens were finally viewed using an ISI-DS 130 dual stage scanning electron microscope (International Scientific Instruments, Buxton, UK).

For light microscopy, each specimen was placed into formal saline for 1 h. Further processing entailed fixing in ethanol for 2 min, washing twice with water, and finally staining for 3 min with toluidine blue (Sigma). The graft surface was then inspected for degree of coverage with endothelial cells, as determined by the percentage covered by blue staining. Areas of graft not covered by endothelial cells did not take up stain.

Statistics

Results are given as mean(s.d.) unless otherwise stated. Comparisons of cell retention at similar times between groups were made using Student's t test.

Results

Labelling efficiency and seeding efficiency

The overall labelling efficiency for all four groups was 50·4(10·2). Seeding efficiencies for the groups are shown in *Table 1*. There was no difference between the seeding efficiencies within each incubation group. Comparing the seeding efficiencies between the LONG and SHORT incubation groups, however, there was a very significant difference ($P < 0{\cdot}0001$).

Cell retention

The cell retention on the grafts at the different flow rates is shown in *Figure 3*. At both flow rates, the LONG seeding procedure gave significantly better cell retention than the SHORT procedure ($P < 0{\cdot}01$ at all times). There was no difference in cell retention between 100 and 200 ml/min in the LONG groups ($P > 0{\cdot}01$). There was, however, a significant difference within

Table 1 *Seeding efficiencies for the four groups*

Seeding type	Flow rate (ml/min)	Seeding efficiency* (%)			
SHORT	100	41·9(6·9)	n.s.	39·5(4·4)	$P<0·0001$
SHORT	200	37·2(5·1)			
LONG	100	81·6(4·5)	n.s.	81·1(6·4)	
LONG	200	80·6(4·4)			

* Values given are mean(s.d.); NS, not significant. Significance was determined using Student's *t* test

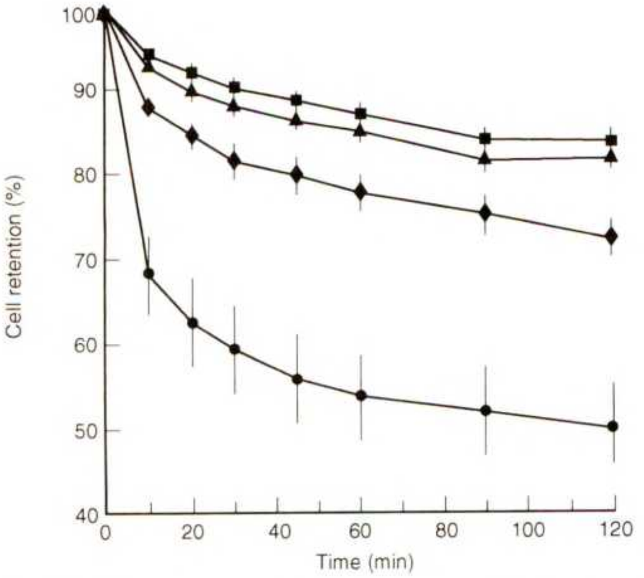

Figure 3 *Graph showing the percentage cell retention at flow rates of 100 and 200 ml/min:* ■, LONG, *100 ml/min;* ◆, SHORT, *100 ml/min;* ▲, LONG, *200 ml/min;* ●, SHORT, *200 ml/min*

the SHORT groups, with more cells detaching at the higher flow rate ($P<0·01$).

Qualitative assessment of grafts

Toluidine blue staining of the graft surface immediately after flow (at 2 h) showed uniform and confluent cell linings in the LONG seeding groups at both flow rates (*Figure 4a*). On the other hand, the coverage in the SHORT seeding group was poor at both flow rates (*Figure 4b*), much of the graft surface being devoid of endothelial cells. Scanning electron microscopy of post-flow samples again confirmed this pattern of cell retention (*Figure 5*).

Discussion

Although we have previously shown[1] that endothelial cells attach very well to fibronectin-coated PTFE, the main criteria for their use in vascular graft seeding is that they remain attached once blood flow is reinstated. In the experiments described above, we have shown that endothelial cells that are seeded acutely over a 20 min period, a method comparable to those used by most groups at present, not only have a poor seeding efficiency, but are detached easily. If the cells are seeded by the method involving overnight incubation on a roller table, the seeding efficiency is greatly improved and the cell attachment in flow is also significantly better. Qualitative assessment of the grafts by scanning electron microscopy and light microscopy confirms this finding. In essence, the acutely seeded grafts start with a scanty covering of endothelial cells and many of these cells are detached when exposed to the shear stresses of blood flow. This is especially marked at flow rates around 200 ml/min.

This phenomenon of significant cell loss after immediate seeding has also been found by a number of other workers. Vohra *et al.*[4] found that, after 2 h of flow at 200 ml/min, almost 50 per cent of seeded cells had been lost from fibronectin-coated PTFE. They used tissue culture medium, rather than blood, in the circuit. It has previously been shown that cell losses during perfusion with acellular perfusate are significantly lower than those obtained using blood[5]. Most workers examining cell losses *in vitro* have used tissue culture medium, so it is difficult to make a direct comparison with the present results. One would, however, expect relatively greater cell losses in our experiments. Even when they seeded with supraconfluent densities over a 90 min period, Vohra *et al.*[6] still found only a 55 per cent cell retention after 2 h flow at 200 ml/min. They did, however, report better retention if preclot was used as an attachment factor. Schneider *et al.*[7] also found that acutely attached cells were poorly retained in flow.

A number of workers have examined cell losses from grafts *in vivo*, and in some cases *ex vivo*, using a canine model. Patterson *et al.*[8] found, using fibronectin-coated PTFE, that 33 per cent of cells were lost in the first 15 min, and by 90 min 45 per cent of cells had detached. Rosenman *et al.*[2] also found a high loss (30 per cent) in the first 30 min. Between 30 min and 24 h there was a loss of nearly 4 per cent per hour, resulting in only 17 per cent of seeded cells remaining attached at 24 h. Ramalanjaona *et al.*[9] also noted a high rate of cell loss in the first 30 min, which subsequently slowed between 30 min and 24 h. No additional losses were seen after 24 h, but by this time 54 per cent of seeded cells had already been lost.

In an effort to reduce cell losses, a number of workers have used confluent layers of endothelial cells. In most cases,

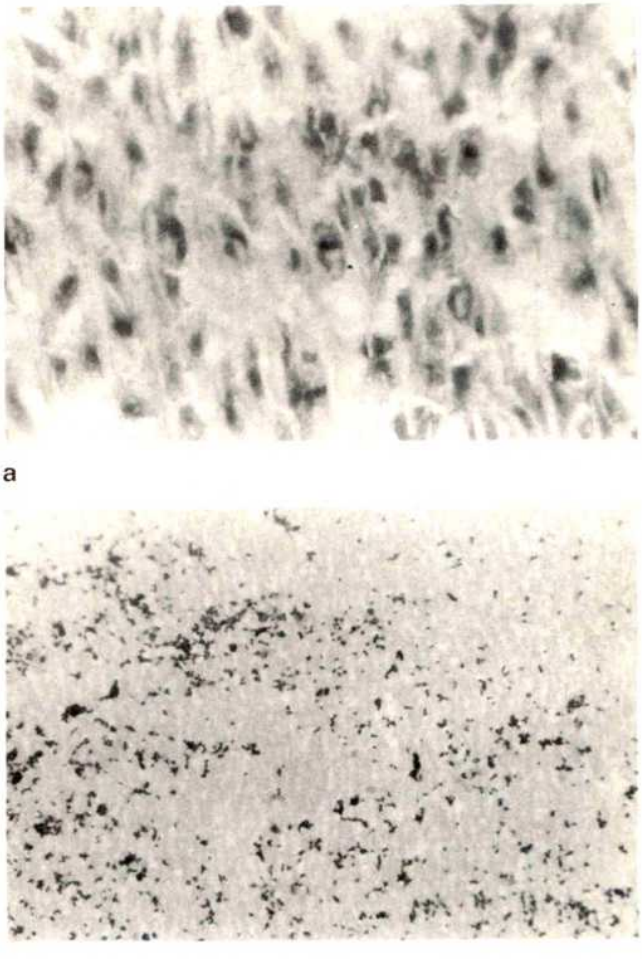

Figure 4 *Toluidine blue staining of seeded grafts after 2 h flow at 200 ml/min:* **a** LONG (*original magnification* × *160*), **b** SHORT *method of seeding* (*original magnification* × *40*)

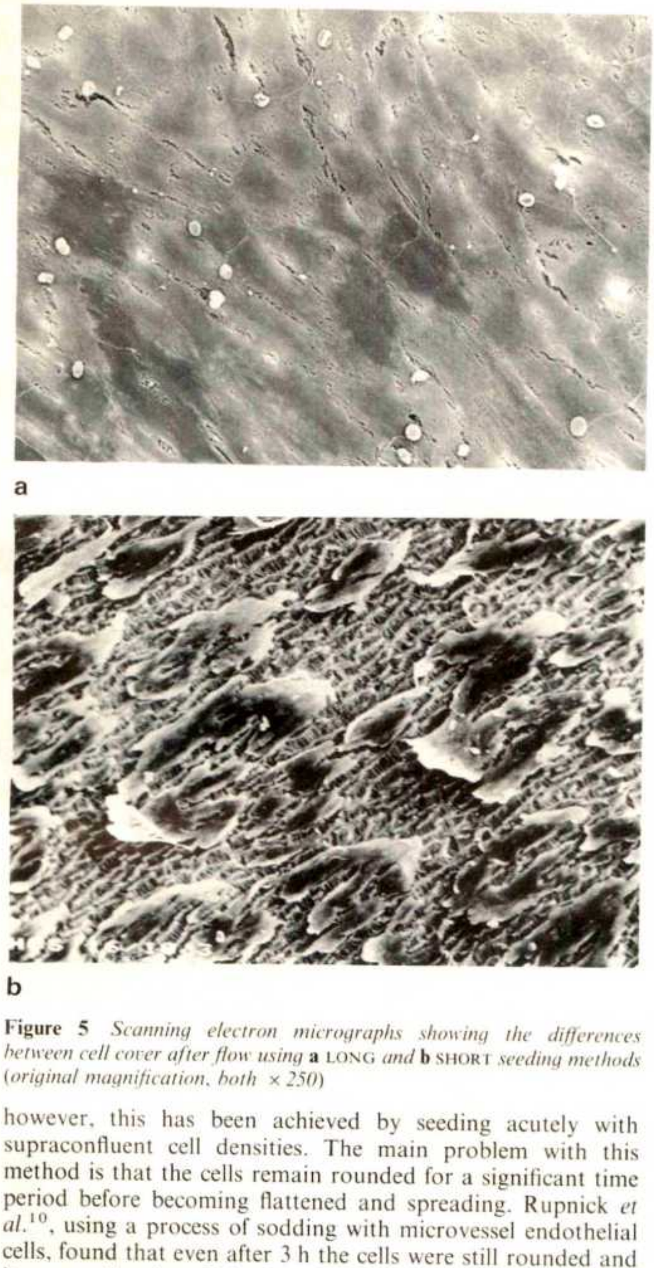

Figure 5 *Scanning electron micrographs showing the differences between cell cover after flow using* **a** LONG *and* **b** SHORT *seeding methods (original magnification, both* × *250)*

however, this has been achieved by seeding acutely with supraconfluent cell densities. The main problem with this method is that the cells remain rounded for a significant time period before becoming flattened and spreading. Rupnick *et al.*[10], using a process of sodding with microvessel endothelial cells, found that even after 3 h the cells were still rounded and it was only after 24 h that they showed signs of uniform spreading and close cell-to-cell association. Anderson *et al.*[11] concluded that optimum immediate confluent endothelial coverage of small-calibre vascular grafts requires a high concentration of cells, attachment to precoated grafts, and several hours' incubation. In theory, rounded cells should detach more easily in flow situations compared with the flattened cells obtained after longer incubations. This would, indeed, appear to be the case; the few experiments that have examined the reaction of flattened cells have shown significantly less detachment than that from acutely seeded grafts. Sentissi *et al.*[12] found that only 11 per cent of cells were lost after 1 h in a flow of 200 ml/min. Schneider *et al.*[13], using preformed layers of human umbilical vein endothelial cells in baboons, showed 81 per cent retention after 1 h. Prendiville *et al.*[14], in an *ex vivo* canine model, found 75 per cent retention of cells at 2 h at 225 ml/min. The main problem with most of these methods, however, is that they entail long periods of cell culture on the graft itself and this is accompanied with some increase in the risk of infection. If the amount of time that the endothelial cells remain on the graft before implantation can be kept to a minimum, but still allowing time for the cells to spread and flatten, this risk is reduced. Anderson *et al.*[11] showed, in a static system, that the longer the cells were maintained on the graft, the more likely they were to detach spontaneously. If, however, a slight shear stress was applied to the cells, they could be maintained for much longer periods.

The method of seeding devised in Leicester uses a relatively short overnight incubation, allowing the cells to become confluent and flatten, combined with a small shear stress imposed on the cells by the slow rotation. Using this method, after 2 h exposure to blood flow, over 80 per cent of the seeded cells still remain on the graft even at a flow of 200 ml/min. Even though some of the more loosely attached cells have detached, the luminal surface still exhibits a confluent monolayer of endothelial cells. As in previous studies, the majority of cells detach within the first 30 min; thereafter, the rate of detachment slows considerably. By the time 2 h is reached, cell detachment appears to have reached a plateau at both flow rates. This did not seem to be the case with the acutely attached cells, although the experiment did not go beyond 2 h. These cells still appear to be detaching at this time, although at a relatively slow rate. The rates chosen in the *in vitro* situation above are comparable with the flow rates seen in femoropopliteal bypasses in a clinical setting[15].

In conclusion, acutely attached endothelial cells not only have a poor seeding efficiency but are also unable to withstand the shear stresses associated with physiological blood flow. To provide the optimum luminal surface for cell seeding, we suggest a two-stage procedure. First, the cells are harvested from a section of autologous vein and grown up in tissue culture flasks over a period of about 1 week. Second, the cells are seeded onto a fibronectin-coated graft, using the overnight incubation method described. The seeded grafts can then be implanted. Although this is more prolonged than the immediate seeding method, it guarantees that the minimum area of graft is left uncovered by endothelial cells. It is also less prolonged than the other methods so far described, which profess to give flattened confluent linings. Regarding the first stage, Watkins *et al.*[16] and Jarrell *et al.*[17] have both shown that it is possible to increase endothelial cell numbers significantly in *in vitro* cell culture. In the present experiments, we have shown that, once cells have been allowed to form a confluent monolayer on the graft using overnight incubation, they remain in this configuration even under the shear stresses of physiological blood flow.

Acknowledgements

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Short note

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Streptococcus bovis septicaemia associated with uncomplicated colonic carcinoma

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Over the past 15 years *Streptococcus bovis*, a Lancefield group D non-enterococcal organism, has become increasingly recognized as a common cause of endocarditis, accounting for 14 per cent of cases of microbial endocarditis[1]. Moreover, a strong association between *S. bovis* bacteraemia and underlying gastrointestinal neoplasm has become evident[2]. To emphasize this association, which has received little attention in the surgical literature, we report a series of six patients with *S. bovis* septicaemia of whom five were subsequently found to have underlying colonic carcinoma, three of whom had no gastrointestinal symptoms at the time of presentation with septicaemia.

Patients and methods

Dumfries and Galloway Royal Infirmary serves a population of 147 000. During the period 1982–1989, 560 patients had clinically significant positive blood cultures, of which 23·5 per cent involved streptococcal organisms. All streptococcal blood culture isolates were further identified using the API 20 STREP system shown in *Figure 1*. *S. bovis* was identified from blood cultures of six patients (four were *S. bovis* biotype I and two were *S. bovis* biotype II). All six patients presented primarily with *S. bovis* septicaemia to the acute medical wards and the case histories are detailed in *Table 1*. The six cases are summarized below (the first case has been reported previously[3]).

Results

There were two women and four men with an average age of 69 years. All six presented with fever and malaise and were found to have *S. bovis* septicaemia. Four patients had clinical and echocardiographic evidence of probable endocarditis and one had histological evidence of endocarditis. Two had had previous valve replacement (cases 1 and 3). All responded rapidly to intravenous penicillin and an aminoglycoside, although patient 2 subsequently required aortic valve replacement for valve rupture.

At the time of presentation, two patients (cases 3 and 5) were noted to have iron deficiency anaemia and one (case 1) to have intermittent rectal bleeding; these three were found to have colonic carcinoma. In patient 3, iron deficiency anaemia had occurred a year previously but responded to treatment, and barium enema and meal were normal; at the time of admission with *S. bovis* septicaemia, a caecal carcinoma was found by colonoscopy. Patient 4 developed iron deficiency anaemia 2 months after *S. bovis* septicaemia, but barium enema was normal; the anaemia recurred a year later after stopping iron therapy and a repeat barium enema then demonstrated a caecal carcinoma. Patient 6, who at no time had had any gastrointestinal symptoms, had three barium enemas and a colonoscopy over the succeeding year (because of the *S. bovis*/colonic neoplasia association) before a 2 cm diameter Dukes' A classification caecal carcinoma was detected. Patient 2, who was not found to have a colonic neoplasm on rigorous investigation, had a splenic abscess from *S. bovis*, requiring splenectomy.

Four of the tumours were in the caecum and one was in the sigmoid colon. One tumour was Dukes' A classification (involvement of mucosa and submucosa only), two Dukes' B and two were Dukes' C. All the tumours were easily resectable and none was complicated by perforation or obstruction.

Discussion

Until 15 years ago, *S. bovis* isolates were rarely reported from humans[4]. Isolates now identified as *S. bovis* were often classified in the past as enterococci because of their ability to grow in bile and to hydrolyse aesculin, or as *S. viridans* because of their colonial appearance, sensitivity to penicillin, and inability to grow in 6·5 per cent saline broth[4]. Whereas previously full identification of a streptococcal species required elaborate, expensive and time consuming tests[5], nowadays streptococci can be easily identified using a multitest strip, API 20 STREP system (Appareils et Procedes d'Identification, Montalieu Vercieu, France), which has been widely available in the UK since 1982.

Endocarditis caused by *S. bovis* was first described[6] in 1945 but it was not until the 1970s that a strong association between *S. bovis* bacteraemia and endocarditis was noted[7]. *S. bovis* accounts for one-seventh of all cases of endocarditis, and two-thirds of reported patients with *S. bovis* septicaemia have associated endocarditis[8]. All the patients in our series had clinical evidence of endocarditis.

The first reported case[9] of streptococcal septicaemia in association with colonic carcinoma was in 1951. It was not until 1977 that a specific association between *S. bovis* and colonic carcinoma was recognized, when Klein *et al.* reported a retrospective series of six cases[10] which they later confirmed with a prospective series of 29 patients with *S. bovis* septicaemia, of whom eight had colonic carcinoma[2]. Since then there have been five retrospective series[1,11–14] of *S. bovis* septicaemia reported in the literature (*Table 2*). All of these have confirmed an association with colonic carcinoma with an incidence rate of 6–28 per cent. The present study shows the closest association, with five of six patients with septicaemia found to have an underlying colonic carcinoma. A similarly high incidence was found in Edinburgh Royal Infirmary during the period 1988–1990; three of four patients with *S. bovis* septicaemia were found to have occult colorectal carcinoma, and the fourth had a large tubulovillous adenoma (personal communication). The high incidence of tumours in our series

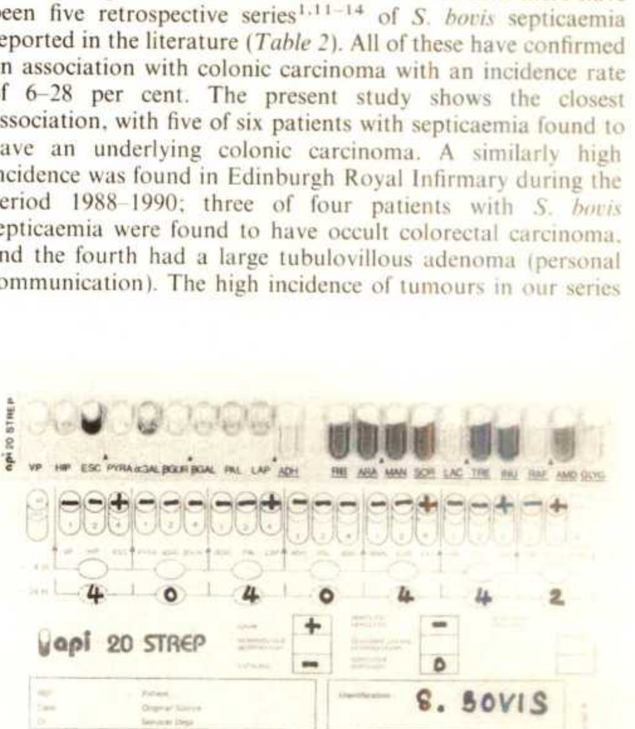
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Figure 1 *Multitest strip used for speciating streptococci by a series of biochemical tests (API 20 STREP system), showing a typical profile of* Streptococcus bovis

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Table 1 *Summary of six patients presenting with* Streptococcus bovis *septicaemia during the period 1982–1989*

Case	Sex/age	Presentation	Endocarditis	Signs and symptoms	Investigation	Delay of diagnosis of tumour	Site of colonic tumour	Dukes' classification of tumour	Follow-up
1	F 60	Fever and toxic confusional state	Probable	Rectal bleeding	Sigmoidoscopy, barium enema	None	Sigmoid	C	Died 2 years later from myocardial infarction
2	M 63	Fever, malaise, left upper quadrant pain	Definite	—	Barium enema, laparotomy	—	—	—	6 years, alive and well
3	M 78	Fever, malaise	Probable	Anaemia	Barium enema, barium meal, colonoscopy	None	Caecum	C	2½ years, alive and well
4	F 70	Fever, toxic confusional state	Probable	Anaemia 2 months later	Barium enema (× 2)	1 year	Caecum	B	2 years, alive and well
5	M 68	Fever, cardiac failure	Probable	Anaemia	Barium enema	None	Caecum	B	1 year, alive and well
6	M 76	Fever, malaise	Probable	None	Barium enema (× 3), colonoscopy	1 year	Caecum	A	6 months, alive and well

Table 2 *Published series of patients with* Streptococcus bovis *septicaemia, showing number with associated colonic carcinoma, adenomatous colonic polyps (excluding those with carcinoma), and total number with colonic neoplasia*

	No. with septicaemia	No. with carcinoma of colon	No. with colonic polyps	Total number with colonic neoplasia
Murray and Roberts[1]	36	2 (6)	6 (17)	8 (22)
Klein *et al.*[2]	29	8 (28)	4 (14)	12 (41)
Reynolds *et al.*[11]	19	2 (11)	4 (21)	6 (32)
Beeching *et al.*[12]	12	3 (25)	5 (42)	8 (67)
Honberg and Gutschik[13]*	90	13 (14)	?	?
Leport *et al.*[14]	34	6 (18)	6 (18)	12 (35)
Present series	6	5 (83)	0	5 (83)

Values in parentheses are percentages. * Short report based on Danish Cancer Registry

and that noted at Edinburgh Royal Infirmary is difficult to explain, but may be the result of our awareness of the association, close liaison with a clinically orientated bacteriologist, and exhaustive investigation to search for an occult colonic neoplasm. Additional weight to the *S. bovis*/colonic neoplasia association is given by the finding of a significantly higher faecal carrier rate of *S. bovis* in patients with colonic carcinoma compared with control patients (55 per cent *versus* 10·5 per cent)[10].

Previous series[1,2,11–14] also demonstrated an association between *S. bovis* septicaemia and colonic adenomatous polyps; these were found in 14–42 per cent of cases (*Table 2*) and up to 67 per cent[14] of patients with *S. bovis* septicaemia undergoing colonoscopy. There are only a few reports of *S. bovis* septicaemia in association with other inflammatory and neoplastic conditions of the gastrointestinal tract[1,12].

This series demonstrates that *S. bovis* septicaemia may sometimes be associated with early tumours; there were one Dukes' A and two Dukes' B carcinomas despite the fact that they were not diagnosed until a year later. The study also suggests a particular association with right-sided colonic lesions; there were four tumours arising in the caecum, and only one in the sigmoid colon. In other reported series[1,2,11–14] information on the site of tumour was available for only 18 patients; ten were in the right colon, one in the transverse colon, two in the sigmoid and five in the rectum.

The mechanism behind the specific association between colonic neoplasm and *S. bovis* septicaemia remains obscure. Kaplan *et al.*[15] have identified an antigen specific to *S. bovis*, termed common (c) antigen, and they postulate that this antigen might be involved in attachment of the infecting organism to colonic neoplasms and to valvular tissue. The biology of common (c) antigen merits further study because of the strong relation of *S. bovis* to such major illnesses as colonic cancer and endocarditis.

In conclusion, this series confirms the previously reported association between *S. bovis* septicaemia and underlying colonic carcinoma. The finding of bacteraemia from *S. bovis* should prompt rigorous investigation to exclude both endocarditis and tumours of the large bowel.

Acknowledgements

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Br. J. Surg. 1991, Vol. 78, July, 885–886

Major limb amputation in northern Nigeria

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The amputation of a limb is always distressing, but the consequences of this loss can be devastating in the developing world where it is often impossible to obtain a prosthesis and a large extended family may be dependent on the patient for their livelihood[1]. This study was carried out to determine the type of amputations performed and their indication, with particular emphasis on those that might have been prevented.

Patients and methods

The University of Maiduguri Teaching Hospital receives patients from the whole of North Eastern Nigeria and, although planned as a tertiary referral centre, surgical facilities in the rest of the region are limited so that the hospital receives a large proportion of both routine and more complex cases. The hospital has a well appointed medical records department with trained staff. This study is a retrospective analysis of all patients undergoing major limb amputation over a 5 year period.

Results

There were a total of 51 major limb amputations, 37 lower limb and 14 upper limb; this represents 0·47 per cent of all operations done during the time of the study. The most frequent sites of amputation were above and below the knee. There were 33 male patients and 18 female patients (mean age 38 years, range 2 weeks to 60 years), people in the prime of life with maximum family responsibilities and earning capacity.

Table 1 *Level of amputation and indication*

	Level of amputation									
Indication	A/K	B/K	Symes	M/T	S/D	A/E	T/E	B/E	T/W	Total
Malignancy 21 (41%)										
Squamous cell carcinoma	5	6			1					12
Sarcoma	6									6
Malignant melanoma			2	1						3
Trauma 19 (37%)										
Post traumatic gangrene	3	1			2	4		2		12
Trauma		2		1		1	1		2	7
Diabetic gangrene		3		1						4
Chronic osteomyelitis	2									2
Mycetoma		2								2
Burns								1		1
Benign ulcer	1									1
Congenital	1									1
Total	18	14	2	3	3	5	1	3	2	51

A/K, above knee; B/K, below knee; M/T, mid-tarsal; S/D, shoulder disarticulation; A/E, above elbow; T/E, through elbow; B/E, below elbow; T/W, through wrist

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The commonest indications for amputation were malignancy in 41 per cent and trauma in 37 per cent. Of the 14 upper limb amputations 12 (86 per cent) were secondary to trauma, often in children. Road traffic accidents were the commonest cause of lower limb injury. There were two amputations for mycetoma. There was not a single case of peripheral vascular disease (*Table 1*).

Discussion

The commonest indications for amputation were malignancy and trauma, accounting for 78 per cent of all the amputations. Of particular note are two groups of patients in which early appropriate management may have avoided amputation; those with squamous cell carcinoma and those with post-traumatic gangrene.

Squamous cell carcinoma is a slow growing tumour[2], usually arising in a chronic tropical ulcer, and indeed the length of history in this series ranged from 1 to 20 years, with a mean of 8 years. Tropical ulcers can be cured by excision and grafting, while an early squamous cell carcinoma can be cured by local excision.

Twelve patients (24 per cent) presented with post-traumatic gangrene, eight in the upper limb. Patients usually consult a traditional healer first[1]. Unfortunately healers do not recognize and do not refer problems beyond their ability, a situation found in other developing countries[3]. Only when the limb is beyond salvage do they turn to a doctor. Accurate reduction and debridement of compound fractures would save many of these limbs.

Patients will continue to consult traditional healers; it would be in the interests of the patients if these healers were taught the symptoms and signs of acute ischaemia, and referred those with compound fractures or non-healing ulcers. Notable is the absence, in this series, of amputation for peripheral vascular disease; this is probably due to the small number of elderly in this community and the small number of smokers.

Acknowledgements

We would like to extend our thanks to the staff of the medical records department at the University of Maiduguri Teaching Hospital.

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Case report

Br. J. Surg. 1991, Vol. 78, July, 886–887

Isolated testicular pain: an unrecognized symptom of the leaking aortic aneurysm

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Leaking aortic aneurysm remains a challenge in diagnosis and treatment. One factor in the high mortality rate associated with this condition is delay in diagnosis and referral for specialist treatment. Although some patients present with collapse and sudden death[1] due to anterior rupture, those with an aneurysm that leaks posteriorly or laterally may complain of severe backache or renal colic. We report a previously unrecognized symptom of the leaking or rapidly expanding abdominal aortic aneurysm, severe testicular pain, which may divert the unsuspecting clinician's attention from the potentially lethal cause.

Case reports

Case 1

A 68-year-old man presented with severe bilateral testicular pain of 6 h duration. He had previously enjoyed good health apart from one episode 2 weeks previously when, after a meal, he vomited and developed an ache in the testes lasting 1 h. The testes were noted to be normal and not tender. Abdominal examination revealed a tender aortic aneurysm which measured 13 cm on plain radiograph. An emergency laparotomy was performed and on opening the aneurysm sac the anterior longitudinal spinal ligaments were visible, suggesting imminent rupture. An 18 mm straight Dacron® graft (E.I. du Pont de Nemours and Company, Wilmington, Delaware, USA) was inlaid into the aneurysm sac. The patient made an uneventful recovery and is alive and well 6 months later.

Case 2

A 67-year-old man was noted 5 years previously to have a 5 cm calcified abdominal aortic aneurysm which remained unchanged in size on regular clinical and ultrasound assessment. Five days after one of his regular clinic attendances he developed severe left testicular pain. On admission, 4 h later, he had developed abdominal pain also on the left side. On examination he was found to have a tender aortic aneurysm and normal testes. At laparotomy the aneurysm was found to have leaked posteriorly on the left side. A 22 mm woven Dacron bifurcation graft was sewn between the aorta above, the common femoral artery on the right, and the profunda femoris artery on the left. He made an uneventful recovery with good popliteal pulses.

Case 3

This man presented with severe testicular pain. On examination the testes were normal to palpation. Later that evening the patient developed abdominal pain and collapsed at home and was immediately admitted to hospital where he was found to have an unrecordable blood pressure with a pulse of 100/min and a distended abdomen. He was transferred immediately to theatre where a laparotomy confirmed an anterior rupture of an aortic aneurysm, with a large retroperitoneal haematoma. An aortobifemoral graft was inserted and he made an unremarkable recovery, leaving the hospital 12 days after the event.

Discussion

Each of these cases presented with a unique symptom of isolated severe testicular pain. This symptom has once before been

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reported in association with an iliac aneurysm[2], but has not been described in isolation as the only symptom of an abdominal aortic aneurysm. It is important to reduce any delay in diagnosis of acute aneurysm and referral of the patient to a vascular surgeon. It is not uncommon, even when the patient has reached hospital, for the aneurysm to be overlooked by the admitting staff, all of whom should be aware of unusual symptoms of aneurysm.

Severe testicular pain has not been previously described as a symptom heralding the imminent rupture of an abdominal aortic aneurysm. The mechanism of pain referral to the testes may be sudden posterolateral expansion of the aneurysm pressing on the visceral afferent pain fibres from the testes. These are relayed from the pelvic splanchnic nerves through the inferior hypogastric plexus, the hypogastric plexus and lumbar splanchnic nerves to reach their cells of origin in ganglia on the dorsal roots of the lower thoracic and lumbar nerves (T9–L1)[3]. These lumbar splanchnic nerves pass through the psoas muscle and it seems likely that lateral expansion of the aneurysm produces the pain referred to the testes. Many patients develop severe back pain when their aneurysm starts to rupture and this may mask pain referred to the testes.

Acknowledgements

The authors would like to thank Dr J. Pattern FRCP for his advice on the neurophysiology of testicular pain.

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Torsion of the spleen managed by splenopexy

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Torsion of the spleen occurs when the organ is congenitally devoid of its peripheral attachments and has an abnormally long vascular pedicle, a condition sometimes known as wandering spleen. Wandering spleen was identified in only two of 1003 splenectomies performed at the Mayo Clinic over a 40-year period[1]. Torsion of the spleen is rarer still, with some 100 case reports in the world literature.

In the event of torsion of the spleen presenting as an acute abdominal condition, the correct diagnosis is seldom made before operation[2]. Splenectomy has been the recommended treatment of choice.

Case report

A 7-year-old girl presented with a 2-day history of generalized abdominal pain and diarrhoea. On examination, she had a temperature of 38·5°C, with guarding and tenderness over the left hypochondrium and flank. There was mild abdominal distension with increased bowel sounds. Plain abdominal radiographs revealed a soft tissue mass in the left hypochondrium (*Figure 1*).

A barium enema, performed to rule out intussusception, demonstrated that the mass was mobile and lay outside and above the splenic flexure. Barium meal showed the mass to be lateral to the greater curvature of the stomach and splenic torsion was diagnosed. At laparotomy the peripheral ligaments of the spleen were absent and the organ had twisted three times on its pedicle. On relieving the torsion, a small area on the antimesenteric border measuring 2 × 2·5 cm regained colour. A splenopexy to the abdominal wall was performed using three collagen stitches. The patient was commenced on penicillin prophylaxis. After operation the blood film remained normal throughout follow-up lasting 1 year. No Howell–Jolly bodies or acanthocytes (irregular erythrocytes suggestive of hyposplenism) were seen. ^{99m}Technetium tin colloid scans performed at 3 and 6 months demonstrated a small area of functioning spleen. Splenic function was estimated quantitatively by examining circulating erythrocytes for membrane pits using phase microscopy[3]. Pit counts were high (>10 per cent) at 3 months, suggesting splenic hypofunction. By 6 months, however, the pit counts were normal (<2 per cent), suggesting recovery of splenic function.

Discussion

Splenic conservation has become important in modern surgical practice in view of the risk of overwhelming postsplenectomy sepsis[4]. Much of the literature on splenic torsion predates

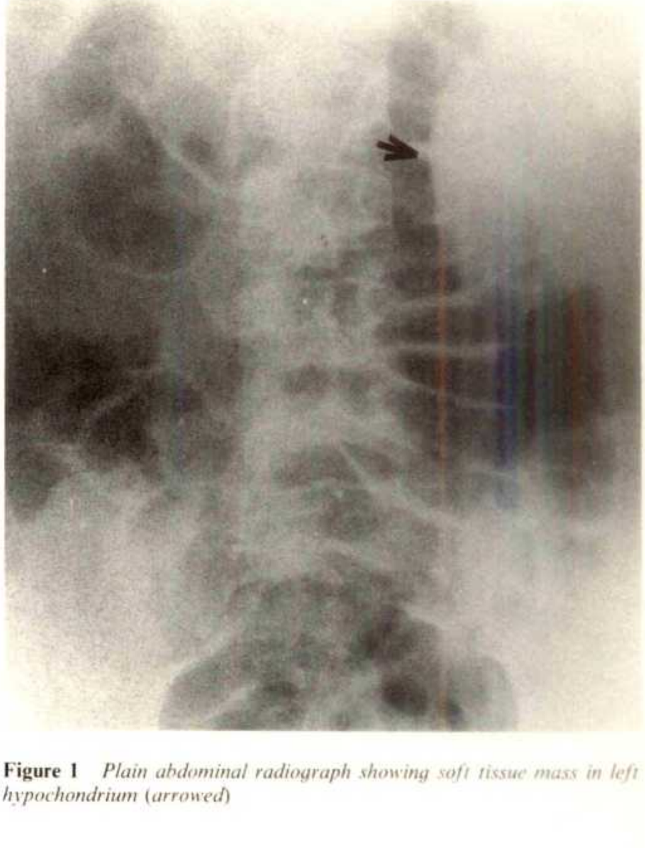

Figure 1 *Plain abdominal radiograph showing soft tissue mass in left hypochondrium (arrowed)*

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recognition of this entity[5]. Hitherto, splenectomy has been uniformly recommended as the treatment of choice. This still applies where the entire spleen is infarcted. However, the increasing availability of modern diagnostic facilities on an emergency basis, as in this case, may lead to intervention before infarction of the whole organ. This case demonstrates that adequate splenic function develops even when a small area of spleen remains viable and that conservation is worthwhile in these circumstances.

Acknowledgements

We acknowledge the help of Dr L. Carroll, Consultant Paediatrician, in the management of this patient.

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Paper accepted 21 January 1991

Erratum

'Groin wound infection after arterial surgery' by D. P. Newington *et al.*, *Br J Surg* 1991; **78**: 617–19.

An editorial error unfortunately led to the omission of the word 'not' from an important sentence in the introduction to the above paper. This sentence should read: 'In consequence, alternative less radical approaches have been developed for deep infections which have not been complicated by haemorrhage, and this retrospective review was undertaken to see if a selective trend towards more conservative surgical procedures is justified'.

We apologise to the authors for this omission and to the reader for any confusion caused.

Correspondence

Pulse oximetry: a new non-invasive assessment of peripheral arterial occlusive disease

Sir

We read with interest the article by Joyce *et al.* (*Br J Surg* 1990, 77. 1115–17) on the subject of pulse oximetry ($P_{\mathrm{sa,O_2}}$) in peripheral vascular disease We assume that the patients and control groups are of comparable mean age, with similar smoking histories, no data are given on this point. More importantly, we find it difficult to understand why pulse oximetry, which reflects arterial oxygen saturation, should be influenced by arterial narrowing. Transcutaneous oximetry clearly mirrors the degree of oxygen utilization in the end-tissue – in other words, it is measuring a function of oxygenation at a level distal to the point at which oxygen is consumed. This is not the case with pulse oximetry, since measurements using this technique rely on the pulsatile nature of pre-capillary flow. Hence the saturation of the blood within the capillaries is not measurable by this method.

Reduced $P_{\mathrm{sa,O_2}}$ readings in peripheral vascular disease may reflect diminished pulsatility in peripheral arterioles. Venous pulsation may therefore contribute a relatively greater proportion to the $P_{\mathrm{sa,O_2}}$ signal, leading to apparently lower arterial saturation Thus the authors may in fact be exploiting a deficiency in the technique to reveal a difference between their control and disease groups which may well be spurious

We would be interested to hear the authors' comments on these remarks.

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Author's reply

Sir

We are indebted to Mr Cheatle and Mr Coleridge-Smith for their interest in our paper and for their informed comments on our study and its findings Their letter raises some issues that we would like to address.

Clearly our control group and patient group were not comparable either in respect of age or smoking history To match the former with the latter would have inevitably included a number of patients with sub-clinical vascular disease Our intention was to utilize a group of healthy people to enable us to establish a baseline of information against which data from patients with peripheral vascular disease could be evaluated.

We did not of course state that there was a direct and simple relationship between oxygen saturation, as measured by pulse oximetry, and arterial narrowing The correlation between $P_{\mathrm{sa,O_2}}$ and angiographic score preoperatively and the maintenance of this relationship postoperatively does, however, suggest an indirect relationship which may very well reflect diminished pulsatility in arterial disease as Cheatle and Coleridge-Smith suggest. Their belief that venous pulsation makes a significant contribution to the $P_{\mathrm{sa,O_2}}$ signal is more putative. We would be genuinely interested in any data bearing on this aspect of pulse oximetry that they can provide. If their contention can be sustained then we shall need to re-evaluate the technique of pulse oximetry and the significance of its derived data Nevertheless, our oximetry values, obtained by a conventional and current technique, are valid in as far as the technique is valid. The significance of the values obtained may of course be subjected to different interpretations.

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Effect of fibrin sealant on the healing colonic anastomosis

Sir

We would like to endorse the findings of Dr van der Ham and colleagues that fibrin sealing of colonic anastomosis does not improve healing (*Br J Surg* 1991, **78**. 49–53) We examined the effect of fibrin sealant (Tisseel, Immuno, Vienna) on a high risk anastomosis model (low anterior resection in mongrel dogs without bowel preparation). Twenty-five animals were randomized to anastomosis with and without fibrin sealant. All were killed on the ninth postoperative day Anastomotic bursting pressure (ABP) measurement followed inspection of the anastomosis for dehiscence and careful removal of all perianastomotic tissue Adhesion formation was graded as follows ○, no adhesions, +, perianastomotic adhesions, + +, widespread adhesions

Two animals died postoperatively, one (fibrin sealant) from sepsis secondary to anastomotic dehiscence and the other (control) from hypovolaemia secondary to intra-abdominal haemorrhage. The results are summarized in the table

Group	Number	Dehiscence	ABP, mmHg mean(s d)	Adhesions ○	Adhesions +	Adhesions + +
Fibrin sealant	12	5	125(25)	0	4	8
Control	12	6	129(22)	2	7	4

As no benefit was found with the fibrin sealant, we were concerned that this may have been due to a reaction to human fibrinogen This now seems unlikely however as Dr van der Ham controlled for such a reaction by demonstrating similar results with both human and rat fibrin sealant in his rat model

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Influence of methylprednisolone on the healing of intestinal anastomoses in rats

Sir

We read with interest Mastboom and colleagues' recent paper (*Br J Surg* 1991, **78** 54–7) examining the effect of steroid therapy on healing ileal and colonic anastomosis in the rat Healing was assessed by the measurement of bursting pressure There are, however, a number of points with which we take issue

At three days no difference could be detected between the bursting pressure of anastomosis in steroid treated and saline treated animals This does not constitute evidence of a lack of effect of steroids on fibroplasia in the intestine. Any wound healing by first intention will have a lag phase during which no tissue bridges the wound space. This lag phase represents the period during which inflammatory cells infiltrate a wound space, capillary budding occurs and finally fibroblasts begin to appear that will deposit collagen and matrix to bridge the tissue gap In fact the lag phase of linear gastric wounds has been shown to be somewhat longer than the usual 2–4 days seen in skin although subsequent gain of wound strength is much quicker[1]. Thus if the effects of steroids *in vivo* are to depress granulation tissue deposition we would only expect to see an effect on wound strength after this initial lag phase during which a wound has little intrinsic strength

At 7 days steroid treated colonic wounds had significantly increased bursting pressures in comparison to control wounds, an unexpected finding. However the authors comment that all wounds tested at this time point burst away from the anastomosis. The tension in the wall of a tube at any particular point is directly related to the diameter at that point at a particular pressure (law of Laplace). Thus if the anastomotic area is less distensible than surrounding bowel (as it is), the tension in the wall of the intestine at an anastomotic site will be much less than in more distensible proximal and distal segments[2]. All that can thus be concluded from the results of 7 days is that the bursting pressures of the anastomosis were greater than those measured. Thus the authors are unable to make any firm conclusions regarding the effect of steroid therapy on intestinal wound healing. It is largely for this reason, the inability of bursting pressure to directly assess anastomotic healing after the first few days, that we have abandoned this model as an experimental technique.

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Author's reply

Sir

We have read with interest the comments of Slavin and Kingsnorth, who state that the measurement of bursting pressure to evaluate anastomotic repair has its limitations. They refer to our recent review[1] on this matter and, obviously, we agree. However, as stated in this review, it may yield valuable information, even 7 days after operation. If one expects a negative effect on repair, and current opinion holds that steroids impair wound healing, a shift in bursting site would be expected. Normal anastomoses would burst away from the suture line, while in the steroid-treated animals rupture would occur within the anastomotic area. This phenomenon does not occur. In addition, steroids would be expected to interfere with collagen synthesis. We have measured significantly increased collagen synthesis in intestinal anastmoses within 24 h after construction[2]. Still, hydroxyproline levels in the anastomoses remained unaffected by steroid treatment. Thus, we feel that our conclusion that short term administration of methylprednisolone does not impair anastomotic healing, as judged by commonly accepted[1] mechanical and biomechanical parameters, is warranted.

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Influence of local hyperthermia on the healing of small intestinal anastomoses in the rat

Sir

We read with interest the paper by Shimizu *et al* describing the influence of peritoneal hyperthermia on small intestinal anastomoses (*Br J Surg* 1991; **78**: 57–9).

There are, however, a number of issues concerning the use of continuous hyperthermic peritoneal perfusion (CHPP) with saline. Examining in a rat model the effect of intraperitoneal saline irrigation at different temperatures on adhesion formation we found[1] that potentially dangerous adhesions are encouraged when the temperature of saline irrigating fluid exceeds 37°C. While the duration of hyperthermic saline irrigation in our model was only 5 min, the number of adhesions at 45°C was significantly higher in comparison with controls. Moreover, the grading of adhesions in one out of 20 animals of this group became more severe (19 slight adhesions, 1 moderate). Using Kendall's τ correlation coefficient we have been able to show a positive correlation between the temperature of saline and the severity of adhesions ($\tau = 0.95$, $P = 0.002$).

Histological findings were characterized by mucosal damage and inflammatory infiltration at the wound edges in the first 3 days and fibrosis and thickening of the muscle layer at later periods. In our model[1], mucosal changes were similar to those described but were combined with adhesion formation[2]. For temperatures of saline up to 50°C the loose connective tissue of adhesions became cellular and compact between the 2nd and 4th weeks, and sufficiently collagenized in the 12th week. These findings explain the tendency[1,2] for persistence of adhesions after the first week in groups irrigated with saline at 45–60°C. The aforementioned persistence of adhesions justifies their potentially dangerous character.

While the authors of this paper used saline at temperatures well above 37°C for 30 min, they made no mention of adhesion formation. The only serious side effect for patients receiving CHPP, according to the authors, is paralytic ileus. Our findings[1,2] suggest that there is a possibility of mechanical obstruction at the temperatures used by the authors. Since reoperation for small intestinal obstruction in a patient previously operated on for cancer is followed by high operative and hospital mortality[3] we would suggest that the authors consider the possibility of adhesion formation in their model before adopting these temperatures in clinical practice.

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Risk of peritonitis and fatal septicaemia and the need to defunction the low anastomosis

Sir

May I be allowed to comment on the apparent abandonment of scientific objectivity and acceptance of inappropriate statistical methodology as illustrated by the article on risk of peritonitis after low anterior resection (*Br J Surg* 1991, **78**: 196–8). The summary and text state a value of $P<0.01$ when comparing serious anastomotic leakage with and without defunctioning colostomy. The two groups were not randomly allocated and no data are presented to show that they were in any way comparable. To apply a statistical test at all is dubious and to use χ^2 with such a small number of events (one in the first group and six in the second) is clearly wrong. If Fisher's exact test is used, $P<0.05$, but some measure of the confidence (or lack of it) is indicted by the fact that just one more event in the colostomy group or one less in the no colostomy group would result in no significant difference at all.

We are told in both the Patients and methods and the Discussion sections that the no colostomy group includes only those patients considered to be at minimal risk of leakage, and yet in the results section we are informed that three of the six leaking anastomses were undertaken in the face of a 'non-curative resection due to extensive local disease'. These statements seem incompatible. One might postulate that a surgeon is less likely to perform a colostomy when incurable disease is present and the prognosis is poor. The high leakage rate in this group may be because of the extent of disease and not the lack of a colostomy.

The authors' conclusion may well be correct, but these data sadly prove nothing.

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Authors' reply

Sir

We respond to the points made by Mr Nixon regarding our article as follows.

We stated at the outset that only patients considered to be at minimal risk were allocated to the non-defunctioned group. To leave patients at high risk of anastomotic leakage in the non-defunctioned group would clearly have been unethical. The results could only therefore have been biased towards less peritonitis in the non-defunctioned group.

Data are presented in the section on Patients and methods that shows that the groups were similar as regards age and sex ratio. Although not mentioned in the text there was no difference in the Dukes' staging between the two groups.

We disagree that it is incorrect to apply any statistical test to the data. In view of overall group sizes ($n=75$ and 125), the application of the χ^2 test is in our view acceptable. Even if Fisher's exact test is used, $P=0.012$, which is highly significant. Using this test, if there had been one more fatal leak in the defunctioned group, $P=0.033$, or if there had been one less fatal leak in the non-defunctioned group, $P=0.028$. Both of these P values are in fact significant. Thus the statement that 'just one more event in the colostomy group or one less in the no colostomy group would result in no significance at all' is untenable. Furthermore, the one fatal leak in the defunctioned group was a freak occurrence whch could, as pointed out, have easily been prevented by washing away the faecal column at the time when the colostomy was created.

In the non-defunctioned group, three of the six fatal leaks occurred in patients who had undergone anterior resection in the face of extensive local disease. In these patients there was doubt as to whether lateral clearance was complete. These patients all underwent total mesorectal excision and the doughnuts were clear of tumour. Leakage in these patients was unlikely to be due to local disease involving the anastomosis. Besides, they were classified and assigned to the non-defunctioned group purely on the criteria stated in the section on Patients and methods and not on the basis of a poor prognosis. In addition, it remains inherently probable that proper defunctioning would have prevented generalized peritonitis.

Finally, we clearly state in the introduction that this paper does not analyse the causes of anastomotic leakage but only the effect on the outcome of the decision to defunction.

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New trends in gallstone management

Sir

Miss Cheslyn-Curtis and Mr Russell mention the rapid recovery and early discharge that may be achieved from short-incision cholecystectomy (*Br J Surg* 1991; **78**: 143–9).

In selected patients, we have also found that this technique gives excellent results. We have also found that the discomfort of the procedure is further reduced by not cutting the rectus muscle, but mobilizing it and retracting laterally.

J. M. F. Clarke

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Study designs and methodology

Sir

We have recently evaluated the scientific standards of publications in physical medicine and rehabilitation. We categorized papers from several journals published in 1990, and have chosen *The British Journal of Surgery* as a reference publication or control group. Therefore we have evaluated the methodology of all therapeutic trials published in the journal in 1990.

A total of 280 articles appeared, 174 (62 per cent) of which were by our definition therapeutic trials. Of these, 75 per cent were conducted without randomization or a control group. Only 5 per cent were blind. Roughly one-fifth had no data on statistical analyses at all, and 10 per cent had failed to define their study population in any way.

We are certainly in no position to criticize surgeons on the methodology of therapeutic trials. Clearly uncontrolled trials can have their place, particularly in surgery. However, randomized trials are the 'only design capable of proving or disproving causality'[1].

It might be (only a weak?) consolation for surgeons to hear that the situation is hardly better in general medicine. 'Although understanding of sound research designs has increased greatly in recent years, we found little evidence that this understanding has been translated into more rigorous designs for clinical research'[2]. This statement dates back more than a decade, but has anything really changed since?

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1 Andersen B. *Methodological Errors in Medical Research.* Blackwell: Oxford, 1990.
2 *N Engl J Med* 1979; **301**: 180.

Book reviews

Surgical Oncology: Current Concepts and Practice

C. S McArdle, ed 240 × 165 mm Pp 332. Illustrated 1990. Guildford: Butterworth–Heinemann £55.

This is an important book as it addresses the management of cancer in a surgical context. Surgical oncology has had a prolonged gestation period in the UK in comparison with its counterpart across the Atlantic. Although now emerging as a new specialty, it is still underdeveloped, and is less readily accepted as such by the surgical fraternity within the British Isles It is welcome, therefore, to see in print a book written predominantly by surgeons with expertise in and a commitment to the further development of the specialty Cancer management, however, requires a multidisciplinary approach, and a number of medical oncologists make an informative and valuable contribution to the management of those malignancies which are treated predominantly by chemotherapy, as well as describing the principles underlying cancer chemotherapy.

Inevitably with a multiauthor book, discrepancies will arise regarding the detailed description and emphasis in different chapters On the whole, the topics are comprehensively dealt with, and current concepts and practice are well enunciated In some sections, different chemotherapeutic regimens are described in too much detail, many of which are of historical interest only. Although radiotherapy is mentioned in the relevant sections, this reviewer felt that a chapter could have been set aside for an exposition by a radiotherapist, delineating the biological rationale for and the clinical uses of radiotherapy in surgical oncological practice. Most, if not all surgeons, not infrequently, will seek advice from, and refer patients to, a radiotherapist for consideration for treatment.

The book has a chapter on recent advances in cancer research, which are outlined in a succinct and readable manner I was disappointed, however, that there was no discussion of certain clinical areas pertinent to the surgeon, e g the roles of preoperative and perioperative nutritional support, and the possible detrimental effect of perioperative blood transfusion Other areas of surgical oncological practice (e g cytology, tumour markers), although described in relevant chapters, could have been discussed more fully in general, as both examples given above are beginning to acquire more clinical importance in the management of many solid cancers In a 'minimalist' era and with a better understanding of basic biological mechanisms regarding tumour cell growth and metastatic dissemination, a critical discussion of 'radical surgery' would have been relevant.

Surgical Oncology is a well written, factually informative, well referenced and authoritative book that documents current surgical oncological practice, at least as practised by some surgeons working (or having worked!) in the northern reaches of Great Britain

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Baillière's Clinical Gastroenterology: Cancer of the Pancreas

J P. Neoptolemos, ed. 229 × 152 mm Illustrated 1990 London. Baillière Tindall. £27 50.

This gem of a book, just 200 pages long and extensively referenced, comes at an opportune time to rationalize and reflect on our therapeutic endeavours in recent years in the treatment of a tumour 'which gives cancer a bad name' The editor should be congratulated on achieving a uniform, economical style by contributors who have not only given a critical analysis of the available literature but also clearly point to the direction for future endeavours.

The chapters on pathology and molecular biology will have an appeal beyond that of the surgeon, and will enable those with an interest in basic research to dig into this volume for extensive background information The three chapters on diagnosis have many practical tips including those on the accuracy of serum diagnostic tests and the reliability of endoluminal sonography (ES). Overstatements are not made, for instance the difficulty in differentiating malignancy from inflammation with ES is clearly stated. Perhaps the chapter on radioimmunolocalization could have been omitted, particularly as the author admits the technique does not have a role in primary diagnosis. The surgeon will invitably turn first to the chapters on resection and will not be disappointed No dwelling here on the dismal results of the past, but rather an upbeat account of the recent success story in lowering perioperative mortality and introducing new reconstructive techniques together with Japanese style extended resections

Finally, the chapters on chemotherapy, radiotherapy and non-operative palliation comprehensively round off this volume in concise style and all for the remarkable price of £27.50 – a must for those with an established interest in cancer of the pancreas, those wishing to development an interest and those looking for the signposts in therapy for the next decade

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Prostate Cancer and Testicular Cancer

D W W. Newling and W G Jones, eds 155 × 235 mm Pp. 348. Illustrated. 1990 New York Wiley-Liss $79.95

This book presents the proceedings of an international consensus conference held at the University of Hull, UK in April 1989 It upholds the tradition of the European Organization for Research on the Treament of Cancer (EORTC) to publish the summaries of knowledge and experience of an international group of clinicians and scientists working in specific areas of interest.

The book is divided into two halves the first concerns prostate cancer and the second testis cancer. Each half includes a group of presentations addressing various aspects of diagnosis and management of the disease, as well as consensus group reports addressing progress and controversies in the subject. The presentations aim to evaluate the basic background knowledge of the subject leading to the present understanding and possible venues for future advances. At a time when advances in clinical knowledge and practice are so swift, the presentations in this book may already be lagging behind However it is a volume that should find its place in the reference section available to clinicians and researchers in the fields of urology, oncology and radiotherpy.

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Treatment of Prostatic Cancer: Facts and Controversies

F H Schroder, ed. 155 × 235 mm Pp 255 Illustrated 1990 New York Wiley-Liss $69 95

This is one of a series of monographs dealing with aspects of the treatment of urological malignancy Prostate adenocarcinoma has been and still is the urological cancer that excites the most interest, and this reflects the uncertainties that surround the subject. Several areas of management of this condition, including the role of radical surgery for early disease and the relative merits of the various hormonal therapies, remain controversial The book was based upon the proceedings of a symposium held under the auspices of the EORTC and therefore probably represents the collected wisdom of some of the world's foremost authorities on prostate cancer

The book is divided into seven parts and interestingly, five deal almost exclusively with advanced disease This reflects the interest of groups such as the EORTC, however, and fails to address in as much detail the problem of local disease The attention of many urological oncologists is now shifting to the question of 'curative therapy', and this will, perhaps, be reflected in future editions

The style of the book consists of written papers paralleling the presentations made at the symposium. This provides a balanced overall view of the clinical work being undertaken by the EORTC genitourinary group

The discussion at the end of each paper takes up more space than its value merits, but does provide useful insight into the disagreements that exist concerning the management of this fascinating condition.

The book should be read by any clinician involved in prostate cancer, if only to make them realize that we cannot be complacent when dealing with this condition. It may be interesting also to review this book again in 10 years or more, to see whether any of the arguments have been resolved.

D. Gillatt

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Operative Urology

F. F. Marshall, ed. 292×216 mm. Pp. 631 Illustrated 1991 Philadelphia. Saunders Publishing. $15.

This latest addition to the library of operative urological textbooks has been edited by F. F. Marshall from the Johns Hopkins Hospital It is essentially an American book, with only a very few of the 92 authors coming from outside the USA. The 85 chapters are arranged within five main sections. adult urological surgery, outpatient surgery, surgery after urological trauma, pediatric urological surgery, and endoscopy and extracorporeal shockwave lithotripsy. This division produces some anomalies. Pyeloplasty, psoas hitch and Boari flap are found in the paediatric section. Transurethral resection of bladder tumours is included under outpatient urology surgery, even though the author suggests that an indwelling urethral catheter may be required for 2 to 3 days after more extensive resections Transurethral prostatectomy is within the adult urological surgery, not the endoscopy section.

The illustrations are a mixture of line drawings, half tones, black-and-white photographs and X-rays The endoscopic section includes a few black-and-white endoscopy pictures but none in colour. The quality of the different types of illustrations is variable. The extent to which text is used to complement illustrations or illustrations are used to highlight text differs from one chapter to another; in the majority the emphasis is on text rather than illustrations. Some authors include considerable background information on presentation, diagnostic techniques, the results of surgery, and quite considerable references. A short editorial comment concludes each chapter, the editor's own contributions escape such an overview, which is unfortunate in the case of the chapter on 'Endoscopic reconstruction of traumatic urethral transections'.

In a specialty where endoscopy plays such a central role it is surprising to find that only about 10 per cent of the book is devoted to the technique The ESWL contribution is very dated, a problem difficult but not impossible to avoid at a time of such rapid changes. Many of the illustrations are disappointingly unhelpful and some of the editorial comments are repetitive and uninspired The text is often verbose as well as lengthy, leading to an overall dilemma in deciding whether this is a textbook of operative urology or of urology

Those who find illustrations the most helpful textbook aid to learning urological surgery will need to look elsewhere, and, if endoscopic urology can be learned from a textbook, better illustrations than are included in this volume, probably some at least in colour, will be needed. It is difficult to predict that this very American book will find much bookshelf space outside North America.

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The Breast, Comprehensive Management of Benign and Malignant Diseases

K. J. Bland, E. M. Copeland III (Eds.) 285×220 mm Illustrated. 1991. Philadelphia· Saunders $88 00

This book sets out to be the definitive 'state of the art' presentation on all aspects of the breast The editors have collected many from the first division of authors Such an enterprise should have produced an outstanding book, that they have failed to do so is due to a number of factors, not least being the number of contributors With so many people being asked to write short sections there has been a problem in collation. Despite the publication date of 1991, there are no references after 1988 and in some chapters very few after 1985 Some sections are dealt with very nicely (David Page's review of the histology, Henry Lynch's section on familial breast cancer) Some sections are slightly dated and others (such as breast reconstruction) are covered in a very cursory fashion.

So, given that this book is already dated, will it find a place on the book shelf? The answer is yes, with reservations I think its use will be by default as there is currently no other tome available It details what was current thinking during 1988, but further reading will be necessary to bring the reader up to date

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Research in Medicine: A Guide to Writing a Thesis in the Medical Sciences

G. Murrell, C Huang, H Ellis 215×135 mm. Pp 105 Illustrated, 1990 Cambridge. Cambridge University Press. £19 50 Hardback. £7.50 Paperback

Any book which provides helpful advice for those embarking on a full time research project is to be welcomed This little volume of 100 pages, enlivened by some delightful cartoons from David Langdon, is an easy and useful read for all those about to start a research appointment

Like all guide-books there is a mixture of the simple and obvious alongside gems of useful information There is a lot of advice on how to get laboratory work under way; emphasis is placed on the importance of good note keeping, planning experiments, compiling references and consulting statisticians

The importance placed on the role of the supervisor in any research project is particulary welcome. The value of careful editing and checking of the final drafts of a thesis is highlighted The use of this book as a checklist of items to be attended to is strongly recommended

No attempt is made to identify the many differences which exist between universities with regard to their higher degrees Some useful information about research opportunities abroad is provided and this is useful The continuing debate over the relative merits of PhD, MD or MCh is identified but not dogmatically dealt with

This volume should help smooth the way for research workers by preventing irritating delays and disappointments and it should also enhance the enjoyment and satisfaction of completing and presenting a worthwhile piece of research.

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Essential Neurosurgery

A Kaye. 229×152 mm Pp. 408 Illustrated 1991 Edinburgh· Churchill Livingstone £15.95

The title of this book sums it up It is a straightforward description of the neurosurgery that should be known by anybody starting a job as a Senior House Officer in the speciality, sitting their fellowship or for that matter their membership of the Royal College of Physicians, as, in practice, the majority of neurosurgical emergencies present initially to physicians It is mainly written by a single Australian author, although there are contributions from two physicians on the managment of stroke and epilepsy It covers the whole range of neurosurgery and, as is essential in a book of this kind, tends to show the reader the black-and-white aspects of the speciality and does not dwell too much on the grey areas. It is very well written and makes easy reading, and the young doctor who reads this from beginning to end will have a very good grasp of the basics of the speciality It competes directly with two books from Glasgow, but is competively priced and anybody who purchases this book should be more than satisfied with it.

P. Richards

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Arterial Surgery of the Lower Limb

P. R. F. Bell 280 × 220 mm Pp 200. Illustrated. 1990 Edinburgh: Churchill-Livingstone £75.00 Hardback

This is a fairly specialized book designed as a technical manual for both the trainee and consultant vascular surgeon. Written by a single highly respected author, it avoids the repetition often seen in multi-author books. Not unnaturally, the book is a personal perspective of the approach to lower limb arterial surgery but this is more than offset by the excellent presentation and well presented chapters. The line drawings througout the book are extremely helpful and illustrate the text with a clarity not often seen.

The book logically progresses through general principles and techniques in the first few chapters to specific procedures which are described in some detail. Emphasis is placed upon reserving vein bypasses for critical ischaemia, quite correctly in my view. The alternatives of reversed vein and *in-situ* saphenous vein grafting are demonstrated and discussed in detail and alternative potential procedures also clearly described.

A major selling point for this book must be the use of the excellent line drawings and descriptive text to describe the approach to virtually all of the accessible vessels in the lower leg. Vascular trainees will find this particularly valuable.

One of the best methods of assessing the potential of a book is to have it examined by several of those at whom the publication is aimed. This book passes the test with flying colours. Although slightly expensive at £75.00, the book deserves a place on the shelves of most trainees and surgeons with a serious interest in vascular surgery.

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Venous Disorders – A Review

J. J. Bergan and J. S. T. Yao, eds 178 × 254 mm. Pp. 576 Illustrated 1991 Philadelphia Saunders $125

This book is an up-to-date and authoritative text edited by John Bergan and James Yao, with contributions from all over the world. It was based on the North Western University faculty course in venous disorders.

Venous Disorders basic considerations of haematological factors, current views on the pathogenesis of venous ulceration, the diagnosis and management of venous thrombosis, and superficial and deep venous insufficiency. The chapters are well referenced and provide a useful source of topical information on almost all aspects of venous disorders.

For those with an interest in venous problems, it represents excellent value.

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Choosing For Children

P. Alderson 196 × 127 mm 1990. Oxford Oxford Paperbacks. £6.99

This book is written for everyone concerned with proxy content for children who are too young to take often difficult and vitally important decisions for themselves at the time of heart surgery. The text is directed towards patients and parents, doctors and nurses, therapists and social workers, chaplains and lawyers, hospital managers, health authority members, and people concerned with parents' and children's interests. The author's practical research for this book was carried out in two large children's heart units in London Teaching Hospitals, both of which are recognized for their pioneering and research efforts in the management of congenital heart defects in infants and children of all ages. The writer's own observations and her many interviews with parents, nurses and medical staff at all levels, are used to illustrate the multitude of problems that confront all parties involved in these matters.

It is important for the public and parents in particular to appreciate that approximately 8 per 1000 live born babies have a congenital heart defect. However, this cohort of babies can be subdivided into three groups which present with different symptoms, at different ages throughout life, and which face quite differing risk factors if and when cardiac surgery is indicated. The first group, consisting of babies having 'simple', usually single defects (small holes in the partitions of the heart, or minor valve deformities) which may never require surgery, or if required at, say, 5 years of age, carries a low risk of mortality (1 per cent hospital mortality). The second group is babies with more serious defects, often a combination of holes and partial obstructions of the valves. These children may require staged surgery or open-heart procedures before going to school at about 5 years of age. The hospital surgical mortality is approximately 5 per cent in this group. Children falling into either of the first two groups may be able to achieve almost normal exercise performance subsequently. Children in the third group have multiple defects in combination. Their natural lifespan is limited without surgery, which is usually a combination of palliative temporizing surgical procedures, and finally a major cardiac reconstruction, sometimes involving the insertion of artificial tubes (conduits) and valves. The surgical risks are high (15–25 per cent risk of mortality), and subsequent exercise performance is probably limited to some extent.

The issues discussed in this book apply to this last group of children in particular. A minefield of dangers and misconceptions is presented and some guidelines towards improving the relationship between parents and medical staff are suggested. It is clear that there is little or no organized training of medical and nursing staff, at all levels, in parent counselling. Methods and interpretation are indivualistic and depend on previous experience, philosophy, religion, compassion and the time factor. Parents must be incorporated more completely into the management team, so that trust can be established with the medical staff at a time when the child is taken out of their hands, and life-giving and life-threatening procedures are undertaken.

I recommend this important contribution to all to whom it is directed. However, many issues remain unanswered. The issues will become even more complex with the growth in transplantation surgery that is anticipated. Awareness, analysis and further debate are indicated.

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Notices and announcements

14–16 July 1991

Techniques in Pulmonary and Oesophageal Surgery

Liverpool, UK

Information Mr R J Donnell, Cardiothoracic Centre, Broadgreen Hospital, Thomas Drive, Liverpool L14 3LB, UK

5–16 August 1991

European Postgraduate Summer Course in Practical Support of the Seriously Ill

Southampton, UK

Information Mr B Moran, Department of Human Nutrition, University of Southampton, Bassett Crescent East, Southampton, SO9 3TU, UK

25–30 August 1991

Hands-On Workshop of Phlebology and Schlerotherapy

Amsterdam, The Netherlands

Information North American Society of Phlebology, 204 N El Camino Real, E-234 Encitas, CA 92024, USA

25–31 August 1991

International Surgical Week

Stockholm, Sweden

Information Scientific Secretariat, 155, Hauptstrasse 63, PO Box 411, CH-4153, Reinach BL1, Switzerland

1 September 1991

European Society for Pediatric Research

Zurich, Switzerland

Information ESPR 1991, c/o AKM Congress Service, PO Box, CH-4005 Basel, Switzerland

1–6 September 1991

6th World Congress in Ultrasound

Copenhagen, Denmark

Information Spadville Congress Service, Sommervaj 3, DK-3100 Hornbaek, Denmark

4–6 September 1991

Oxford 1991, Graft Infiltration Meeting

Oxford, UK

Information Catherine Hughes, Nuffield Department of Surgery, John Radcliffe Hospital, Headington, Oxford OX3 9DU, UK

4–6 September 1991

1st European Conference on Advances in Wound Management

Cardiff, UK

Information Christine Jones, Macmillan Conferences, 4 Little Essex Street, London WC2R 3LF, UK

9–13 September 1991

11th Congress of the European Association for Cranio-Maxillo-Facial Surgery

Innsbruck, Austria

Information Professor Dr R Fries, A-4040 Linz, Pferdebahnpromenade 17, Austria

19–20 September 1991

Tissue Viability Society Autumn Conference

London, UK

Information Mr J Gisby, Tissue Viability Society, Wessex Rehabilitation Association, Odstock Hospital, Salisbury, Wilts SP2 8BJ, UK

20–23 September 1991

60th Annual Meeting of the Royal College of Physicians and Surgeons of Canada

Quebec City, Quebec, Canada

Information Anna Lee Chabot, The Royal College of Physicians and Surgeons of Canada, 74 Stanley, Ottawa, Canada K1M 1P4

24–26 September 1991

5th International Symposium on Colorectal Cancer

Turin, Italy

Information Francorosso Health Congress, c/o Jet Viaggi, Corso Matteotti, 1, 10121 Torino, Italy

2–4 October 1991

12th International Symposium on Computer Assisted Decision Support & Database Management in Anesthesia, Intensive Care and Cardiopulmonary Medicine

Rotterdam, The Netherlands

Information Dr Omar Prakash, Thorax Centre, Erasmus University, 3000 DR Rotterdam, The Netherlands

7–10 October 1991

5th Congress of the European Society for Organ Transplantation

Maastricht, The Netherlands

Information Congress Secretariat, Conference Agency Limburg, c/o University Hospital Maastricht, PO Box 1918, 6201 BX Maastricht, The Netherlands

9–12 October 1991

Principles of Colon and Rectal Surgery

Minneapolis, Minnesota, USA

Information Continuing Medical Education, University of Minnesota Medical School, Box 202 UMHC, 420 Delaware Street Southeast, Minneapolis, Minnesota 55255, USA

20–25 October 1991

American College of Surgeons Annual Clinical Congress

Chicago, USA

Information Sally Gerneski, American College of Surgeons, 55 East Erie Street, Chicago, Illinois 60611-2797, USA

7 November 1991

'Vascular Training Would Be Improved By A Specific Diploma'

London, UK

Information Mr J H N Wolfe, Secretary, London Vascular Debating Group, St Mary's Hospital, Praed Street, London, WC2 1NY, UK

7–9 November 1991

3rd Combined Meeting of the Nederlandse Vereniging voor Thoraxchirurgie and the Deutsche Gesellschaft für Thorax-, Herz- und Gefässchirurgie

Maastricht, The Netherlands

Information Organizing Secretariat, Conference Agency Limburg, University Hospital Maastricht, PO Box 1918, 6201 BX Maastricht, The Netherlands

7–10 November 1991

XVII European Society for Medical Oncology Conference

Lyon, France

Information Michel Clavel, MD, XVII Congress ESMO, CLB, 28, rue Laennec, 69373 Lyon Cedex 08, France

8 November 1991

Vascular Symposium. Angioplasty, Thrombolysis & Angioscopy — A Minimally Invasive Approach to Arterial Disease

Edinburgh, UK

Information Sheila Heap, Meadox (UK) Ltd, Matthew House, Matthew Street, Dunstable, Bedfordshire LU6 1SD, UK

12–14 November 1991

1st European Conference on Tissue Banking and Clinical Application

Berlin, Germany

Information Mr Rudiger von Versen, German Central Tissue Bank, ITT, Medical Faculty (Charite), Humboldt-University Berlin, Schumannstr. 20/21, D-1040 Berlin, Germany

17–23 November 1991

Surgery of the Pancreas, Liver and Biliary System

Edinburgh, UK

Information Courses Department, The British Council, 10 Spring Gardens, London SW1A 2BN, UK

3-5 December 1991

6th International Workshop on Therapeutic Endoscopy

Hong-Kong

Information Dr J W C Leung, Department of Medicine, The Chinese University of Hong-Kong, Prince of Wales Hospital, Shatin, Hong-Kong

12–13 December 1991

1st EEC Conference on Pain Research

Brussels, Belgium

Information M Staquet, Rue Heger-Bordet, 1, B-1000-Brussels, Belgium

3–7 May 1992

7th International Congress of Mastologie

Rhodes, Greece

Information E Soutas, Public Relations Center Ltd, 102 Michalakopoulou Street, 115 28 Athens, Greece

JUNE 1991/VOLUME 161/NUMBER 6

The American Journal of Surgery

OFFICIAL PUBLICATION OF.
The Society for Surgery of the Alimentary Tract
The North Pacific Surgical Association
The Society for Clinical Vascular Surgery
The Society of Head and Neck Surgeons
The Southwestern Surgical Congress
The Association for Surgical Education

Contents

SCIENTIFIC PAPERS

625 **Preoperative Insurance Status Influences Postoperative Complication Rates for Gastric Bypass**
Louis F. Martin, Tjiauw-Ling Tan, Pamela A. Holmes, Dolores A. Becker, John Horn, Lowell D. Mann, and Edward O. Bixler

634 **Editorial Comment**
Joseph M. Civetta

635 **Collagen Stability and Collagenolytic Activity in the Normal and Aneurysmal Human Abdominal Aorta**
Marshall W. Webster, Clyde E. McAuley, David L. Steed, David D. Miller, and Christopher H. Evans

639 **HLA-DR Antigen Expression on Peripheral Blood Monocytes Correlates with Surgical Infection**
William G. Cheadle, Michael J. Hershman, Samuel R. Wellhausen, and Hiram C. Polk, Jr.

646 **Detection of Clinically Suspected Deep Vein Thrombosis Using Light Reflection Rheography**
Alberto A. Mitrani, Marco L. Gonzalez, Mark T. O'Connell, Jorge Guerra, Ronna B. Harwood, and Laurence B. Gardner

651 **Use of Light Reflection Rheography for Diagnosis of Axillary or Subclavian Venous Thrombosis**
MAJ Dipankar Mukherjee, COL Charles A. Andersen, MAJ Anthony S. Sado, and Michael C. Bertoglio

657 **Abnormal Esophageal Transit in Patients with Typical Reflux Symptoms but Normal Endoscopic and pH Profiles**
Craig A. Eriksen, Paul T. Cullen, David Sutton, Norman Kennedv. and Alfred Cuschieri

662 **Role of Renal Sympathetic Nerve Activity in Renal Failure Associated With Obstructive Jaundice in the Rat**
Patricia A. O'Neill, Richard B. Wait, and Kim U. Kahng

668 **Loop Colostomies Are Totally Diverting in Adults**
Don M. Morris and David Rayburn

672 **A Nine-Year Experience with Crossover Femoro-Femoro-Popliteal Sequential Bypass**
Martin I. Ellenby, Alan P. Sawchuk, Thomas H. Schwarcz, Joseph P. Meyer, Jose Montalvo, D. Preston Flanigan, and James J. Schuler

677 **Experience with 225 Hepatic Resections for Hepatocellular Carcinoma over a 4-Year Period**
Kazue Ozawa, Takashi Takayasu, Kaoru Kumada, Yoshio Yamaoka, Kouichi Tanaka, Nobuaki Kobayashi, Takashi Inamoto, Yasuyuki Shimahara, Keiichiro Mori, Kazuo Honda, and Katsuhiro Asonuma

ASSOCIATION FOR SURGICAL EDUCATION

683 **Management of Educational Change in Times of Medical Reorganization**
John L. Provan

HOW I DO IT

687 **Laparotomy Closure Reinforced with Buried Polyglyconate Retention Sutures**
John D. Urschel

BRIEF REPORT

690 **Education About Death and Dying During Surgical Residency**
William Rappaport, Christopher Prevel, Donald Witzke, John Fulginiti, Jeff Ballard, and Thomas Wachtel

REVIEW

693 **Treatment of Compound Fractures**
David Seligson and Stephen L. Henry

ABSTRACTS

703 **SSAT Abstracts**

702 ***The British Journal of Surgery* Table of Contents (vol. 78, no. 5, May 1991)**

720 **Information for Authors**

A14 **Classified Advertising**

A15 **Classified Advertising**

A16 **Society Meetings**

A16 **Announcements**

Br. J. Surg. 1991, Vol. 78, August, 897–899

Justifying arterial reconstruction to crural vessels – even with a prosthetic graft

In Western societies critical limb ischaemia is estimated to affect 500–1000 people per million population each year. The current prognosis for these patients is poor and arguably too few reconstructive operations are performed Crawford Jamieson has calculated that 480 vascular surgeons are required to achieve an adequate service in the UK and, currently, only a handful of surgeons in Britain have a 90 per cent or greater vascular commitment. In Britain 200 operations per million population are undertaken for occlusive arterial disease each year, whereas in Norway and the USA the figures are at least twice as high; 400 and 500 operations per million population per year respectively. A survey of six European Community countries suggests a figure of 360 operations per million population per year[1].

It is estimated that the 5000 new patients referred for limb fitting in Britain each year represent only half the number of amputations being performed[2] since many of this geriatric population are not suitable for remobilization on a prosthesis The majority are therefore confined to house and wheelchair, and their disability conspires to undermine the resources of the Social Services as well as the emotional resources of the patient.

Within Britain, the ratio of arterial reconstruction to primary amputation varies widely between the various health districts[3]. This may be partially explained by regional differences in population structure, but the facilities, time and finances available to the local surgical service are also likely to be important factors. For example, high quality angiography is required to visualize distal vessels in severely ischaemic limbs. This facility is, unfortunately, not universally available, and a failure to identify vessels suitable for reconstruction may lead to inappropriate primary amputation.

The philosophical bias of the local surgeon is another important factor. While proximal arterial reconstruction is well established, it can only account for approximately one-third of reconstructions for critical ischaemia. Although the case for reconstruction involving distal crural vessels is contentious, there is a growing body of evidence demonstrating the value of crural reconstruction using autologous vein to prevent amputation[4,5]. Nevertheless, these operations can stretch both resources and expertise, and sceptics continue to grumble, sometimes correctly, that the results have been laundered For example, it is only very recently that a consensus has been reached on the definition of critical ischaemia[6].

Unfortunately, balloon angioplasty (with or without the use of a laser) currently produces disappointing results when used in infrapopliteal vessels[7] and drug therapy can produce, at best, only a temporary improvement in ischaemic symptoms. Therefore, clinicians are still faced with a choice between amputation and crural reconstruction. Many general surgeons in district general hospitals currently lack the operating time, instruments and other facilities to undertake these protracted procedures. A decision to initiate a programme of grafting to ankle level requires significant expenditure from dwindling theatre and radiological budgets The pressure on operating time increases waiting lists, perhaps prejudicing patients requiring short procedures with a more certain outcome. Each disappointing outcome might result in derision from sceptical medical, anaesthetic and surgical colleagues It is hardly surprising, therefore, that few of these difficult reconstructions are performed outside specialist vascular units. Furthermore, the budgetary changes currently being imposed on the National Health Service might lead to a further reduction in these operations.

Making a cogent case for the use of polytetrafluoroethylene (PTFE) grafts (when no autologous arm or leg vein is available) to crural vessels stretches credibility even further. The lazy abuse of PTFE has led some leading surgeons to deride its use since 'autologous vein should always be found'. This has not been our experience when tertiary referral patients have often had several previous cardiac and peripheral vascular operations. We then have a dilemma of reconstructing with a prosthetic

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material or performing primary amputation – a situation arising in one-fifth of our distal reconstructions.

Reviewing the figures from recent reports of femorocrural regrafting using vein reveals mean 1- and 3-year graft patency rates of 75 per cent (range 47–100) and 62 per cent (range 47–71) respectively. A similar review of the series reporting PTFE graft results produces figures of 43 per cent (range 21–60) and 30 per cent (range 14–38) at 1 and 3 years respectively. At these patency rates the arguments against prosthetic femorocrural reconstruction are overpowering.

In 1984, Miller in Adelaide developed a venous collar to facilitate the distal anastomosis of a PTFE graft and was surprised by the improvement in results[8]. Four years later Taylor developed an anastomotic vein patch technique[9] and also obtained surprisingly good patency rates. We have obtained gratifying results using the Miller collar[10] which has prompted us to examine these complex anastomoses further. *In vitro* studies have shown that these new techniques may have potential anastomotic compliance advantages (dependent on the orientation of the vein segment relative to that of the artery[11]) as well as identifying arterial distortion associated with traditional end-to-side PTFE anastomosis. This distortion is largely prevented by the use of a short venous interposition. Furthermore, we have been able to study failed grafts and have radiological and histological evidence to suggest that the new anastomotic techniques alter the site of deposition of intimal hyperplasia, moving it from critically small recipient arteries to the relatively wide anastomosis between PTFE and vein segment. We have now inserted 55 PTFE grafts (> 70 cm in length) to crural vessels using the Miller collar anastomosis and obtained a 3-year patency rate of 52 per cent. This compares with our patency rate of 78 per cent for vein grafts of similar length. Irrevocable prosthetic graft failure has led to major amputation in all but two patients. Calculations show that the primary amputation rate would have risen from its current figure of 3 to 24 per cent had prosthetic grafts not been used. Furthermore, despite the high incidence of reoperation and the cost of amputation in some patients, this aggressive approach remains cost-effective over a 3-year follow-up period[12]. These experimental and clinical results have led us to modify the venous collar to take advantage of the beneficial features of both the Miller collar and the Taylor patch; the technique is described later in this issue of the *Journal*[13].

The management of patients unfortunate enough to have critically ischaemic limbs who lack sufficient autologous vein for conventional femorocrural bypass grafts demands energy, expertise and resources. Outcome is dependent on adequate preoperative investigation and patient selection, adequate theatre time and resources, as well as improvements in surgical technique. An aggressive policy of reconstruction has the potential to reduce the number of patients whose lives are destroyed by amputation and who, unseen, sap scant financial resources.

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Br J. Surg. 1991, Vol 78, August, 899–900

Management of idiopathic megarectum and megacolon

General and colorectal surgeons, as well as gastroenterologists, are seeing an increased number of adult patients with severe constipation who have not responded to the usual dietary manipulations and laxatives Far from being a trivial symptom, these patients' social and working lives are often limited by abdominal pain and distension, and a poor sense of well being. The final manifestation of markedly decreased bowel frequency hides a complex variety of underlying abnormalities. Different types of severe constipation have a different aetiology, epidemiology, and require a different therapeutic approach[1].

Young women with *severe idiopathic constipation* have a normal bowel diameter and are often most troubled by bloating and pain. The rectum is empty and the underlying disorder is one of failure of colonic peristalsis. Large doses of laxatives are often ineffective in these patients, and colectomy has a variable outcome[2]. The surgical therapy for this condition has been extensively reviewed[3].

Patients with severe constipation and a dilated colon who also have dilatation of their upper gut appear to suffer from *chronic idiopathic intestinal pseudo-obstruction*[4] Recent staining techniques and electron microscopy have demonstrated an abnormality of either the nerve plexuses or one of the smooth muscle coats in most patients[4]. In a third of patients the disorder has a Mendelian inheritance. These patients require not only treatment of their panenteric motility disorder but may also need nutritional support.

Patients with a chronically dilated rectum or colon in whom the upper intestine appears morphologically normal seem to have a disorder confined to the large bowel. Hirschsprung's disease should be excluded by confirming the presence of the rectoanal inhibitory reflex, or by obtaining a full thickness rectal biopsy. Metabolic and other secondary causes of a dilated bowel should also be considered. Ultimately there remains a large group of patients with a dilated large bowel of unknown cause, *idiopathic megarectum and megacolon*. This condition affects males and females in equal proportion, and may have a childhood or adult onset. Recurrent faecal impaction is common and those with a childhood onset often soil. The nerve plexuses and muscle coats appear grossly normal, and the aetiology of the condition remains unknown.

Patients with idiopathic megarectum or megacolon can often be successfully managed with long-term ingestion of laxatives. The osmotic laxative magnesium sulphate keeps the stool semi-liquid and is effective in preventing recurrent impaction However, it has an unpleasant taste. Alternatives include oral lactulose or phosphate enemas. Ultimately surgery is required in those patients in whom laxatives are poorly tolerated or ineffective, sometimes due to a grossly dilated bowel.

Which operations offer the best outcome? Only recently have the surgical results in this group of patients been critically evaluated. In those with a moderately dilated colon, a colectomy with ileorectal anastomosis offers the best results. In a recent series of 40 patients undergoing a colectomy for this condition, 80 per cent achieved a normal bowel frequency and most were relieved of the need for laxatives, the need to strain, and faecal impaction[5]. A third of the patients, however, continued to experience some abdominal pain. After surgery, 85 per cent of the patients felt well or very well. Patients with dilatation of only the left colon or whole colon appeared to

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benefit equally from a subtotal colectomy. The results of an ileorectal anastomosis were superior to those of a caecorectal anastomosis or a sigmoid resection – these operations had a higher incidence of persistent constipation[5].

If the whole colon is dilated, a restorative proctocolectomy with ileoanal anastomosis is an alternative; this has been reported in five patients[6]. All were relieved of their constipation but two required antidiarrhoeal medication. It is not clear that this complex procedure is superior to a subtotal colectomy.

In those with a grossly dilated rectum, the most commonly performed operation has been the Duhamel procedure. Although early reports suggested a favourable result in most patients, the outcome appears to be less satisfactory than when the same operation is performed for Hirschsprung's disease. In a series of 20 patients in whom the rectal diameter in a lateral radiograph ranged from 10 to 14 cm (normal diameter <6·5 cm), half achieved a normal bowel frequency[7]. However, seven patients remained constipated and, of these, five required further surgery for constipation.

If only the distal bowel is dilated, could this be tackled directly? Only one study has examined the results of a distal resection and coloanal anastomosis[8]. Out of seven patients the outcome was good in five. One remained constipated – despite a lack of postoperative bowel dilatation the proximal colon remained hypopropulsive; this patient highlights the need for detailed preoperative motility studies. A further patient died from complications after surgery. This procedure remains experimental.

A simpler alternative to these major resections involves the formation of a stoma. If only the distal colon is dilated, formation of a colostomy using proximal bowel of normal diameter provides relief of the constipation[8].

What should one do with the patient who has had a colectomy but remains constipated? Four such patients who had an end ileostomy created had normal stoma function, although all had some residual abdominal pain[8]. This subgroup of patients may have unidentified small bowel pathology. A restorative proctocolectomy is an alternative[6].

Patients with idiopathic megarectum and megacolon require careful preoperative evaluation. Many are mildly intellectually impaired or have psychological problems. The upper gastrointestinal tract should be studied radiologically, and possibly by more detailed motility studies if available. Colonic transit studies are a mandatory part of the assessment. Surgery in this group of patients is a potential minefield for the unwary.

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Review

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Therapeutic aspects of radio-isotopes in hepatobiliary malignancy

Liver tumours frequently present at a late stage and only a minority of patients are likely to benefit from resection or transplantation. Inoperable tumours carry a grave prognosis. External beam irradiation of the liver is dose-limited by the radiosensitivity of hepatocytes, particularly in the presence of cirrhosis, but internal radiation using radio-isotope sources can achieve more selective irradiation of the chosen field. Sealed sources are dose-limited by their effects on surrounding tissues, whereas with unsealed sources the dose of radio-isotope administered is limited by bone marrow suppression. Iridium-192 wires are most frequently employed as a sealed intracavitary source. They may be inserted surgically, transhepatically or endoscopically. Doses of up to 60 Gy can be delivered to a malignant biliary stricture without damage to the surrounding parenchyma. The incidence of cholangitis is low if treatment is administered after insertion of an endoprosthesis. Unsealed radio-isotope sources may be injected directly into the tumour, administered embolically via the hepatic artery in the form of microspheres or lipid droplets, or given via parenteral infusion attached to tumour-specific antibodies. Of these vehicles, the lipid agent Lipiodol appears to be the most effective and can deliver a potentially lethal dose of radiation to small tumours. Host reaction to the injected antibody remains a major drawback to the use of monoclonal antibodies as targeting agents. Iodine-131 is a β- and γ-emitter, producing a local tumoricidal effect and allowing accurate dosimetry by means of external scintigraphy. Yttrium-90 is a pure β-emitter with a greater maximum β energy and cytotoxic range; however, it is retained in bony tissues, resulting in a dose-related risk of marrow suppression. Bone absorption cannot be measured by external imaging owing to the absence of γ emission. This lack of accurate dosimetry, coupled with the toxic side-effects of yttrium treatment, make iodine-131 the current isotope of choice.

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Although surgery remains the treatment of choice for malignant liver tumours, few patients are likely to benefit from resection or transplantation as most present at a late stage. Resection of primary hepatocellular carcinoma (HCC), a neoplasm which occurs most commonly in cirrhotic livers, is complicated by the problems of major surgery in cirrhotic patients, and survival is significantly worse than in patients without cirrhosis[1]. As a result, the resection rate in HCC rarely exceeds 25 per cent. In a recent series from South Africa, fewer than 1 per cent of patients were deemed resectable[2]. The resectability of other primary liver tumours as a whole is under 10 per cent[3] and that of secondary tumours around 5 per cent[4]. Transplantation has been performed in patients with tumours apparently confined to the liver, but the long-term survival of patients with symptomatic tumours is poor[5] Over 75 per cent of patients transplanted for HCC die within 3 years, the vast majority from metastatic tumour recurrence[6]. Symptomatic hepatic malignancies which are unresectable and unsuitable for transplantation carry a grave prognosis. In a retrospective analysis of 229 oriental patients with HCC who received no specific treatment, Okuda *et al.*[7] reported a median survival of 1·6 months The prognosis in cholangiocarcinoma and metastatic disease is scarcely better. In a review of 57 cases of cholangiocarcinoma proven at autopsy, the median survival was 6·5 months[8]. Jaffe *et al.*[9] recorded a median survival time of 136 days for patients with solitary liver metastases, compared to 93 days for patients with metastases localized to one lobe of the liver and 72 days for patients with widespread metastases. Virtually all patients with untreated metastases are dead within 2 years[10].

In HCC, tumour response to a variety of cytotoxic agents has been reported[11–13], but long-term survival remains disappointing, the cumulative rate rarely exceeding 25 per cent at 1 year. The survival of patients failing to respond to chemotherapy is extremely short[14]. An increased response rate of up to 50 per cent is possible if the cytotoxic agent is selectively infused via the hepatic artery[15–17], but there is no good evidence that the technique prolongs survival[18] Similarly, response rates of around 60 per cent have been reported following continuous intra-arterial infusion of 5-fluorodeoxyuridine in patients with colorectal liver metastases, but no signficant survival benefit was seen at 2 years[19]. Intra-arterial infusion therapy carries a

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significant morbidity in the form of chemical hepatitis and gastrointestinal ulceration. The response to chemotherapy in cholangiocarcinoma is very poor[8]. Embolization[20], liver devascularization[21], cryotherapy[22] and alcohol injection[23] have all been used to palliate inoperable tumours, but there is little evidence of improved survival in any studies to date.

Radio-isotopes in the liver

Radiotherapy is of proven benefit in a wide variety of tumours, both for palliation and radical cure. The radiation is usually administered as a beam of γ rays or high-energy particles derived from an external source (teletherapy). External beam irradiation of tumours in the liver is, however, dose-limited by the relative radiosensitivity of the normal hepatic parenchyma. The maximum therapeutic dose is between 20 and 35 Gy for a healthy liver[24], but doses of this magnitude are associated with a significant incidence of hepatic failure in the presence of cirrhosis[25]. External beam radiotherapy is administered in daily fractions of 200 cGy.

Internal irradiation of hepatic tumours (brachytherapy) may employ sealed or unsealed radio-isotope sources: both offer several avantages over external beam techniques.

1. Sealed sources may be surgically implanted under direct vision, inserted percutaneously under CT or ultrasound guidance, or introduced via an endoscope. More accurate placement of the source results in more selective irradiation of the chosen field, in particular reducing the radiation dose to overlying tissues which would lie in the path of an external beam.
2. Selection of an isotope with appropriate characteristics permits prolonged irradiation and a high cumulative dose to tumour tissue analogous to fractionation, but without a similarly high dose to surrounding parenchyma.
3. Unsealed sources may be injected systemically or selectively infused at angiography. Localization is assessed using γ scintigraphy and/or β probes which also provide accurate information on radiation dosimetry to the tumour and surrounding tissues.

Choice of radio-isotope

Three main isotopes are currently used to treat hepatobiliary malignancies. Iridium-192 is the isotope most frequently employed as a sealed intracavitary source. Iodine-131 and yttrium-90 are used as unsealed sources attached to a variety of vehicles for systemic, intra-arterial or intratumoral injection.

Sealed sources

Iridium-192 wires have largely replaced radium[26] as a source of intracavitary irradiation for hepatobiliary tumours, and have been used extensively in the palliative treatment of malignant biliary obstruction[27–31]. The wires are 1·1 mm in diameter and may be inserted surgically, transhepatically via a 12-Fr percutaneous drain, or endoscopically via a nasobiliary catheter. High dose rates of around 12 cGy/s result in a shorter exposure time than with conventional radium sources. Up to 60 Gy can safely be delivered to a malignant biliary stricture without significant irradiation of the surrounding parenchyma. Iridium-192 has a relatively long half-life of 74 days, necessitating removal of the source after delivery of a therapeutic dose.

In a recent paper by Ede *et al.*[27], a radiation dose of 60 Gy was administered over a mean period of 85 h (range 77–116 h). In common with most authors, this study employed endoscopic insertion. The major drawback of the endoscopic approach is early cholangitis, which occurs in up to 30 per cent of patients treated without, or before, insertion of a biliary endoprosthesis[31]. Ede and his colleagues reported a much lower incidence of cholangitis if treatment was administered 2 weeks after insertion of the endoprosthesis[27] No serious toxicity was observed in 14 patients, and the median survival was 10·5 months from treatment This is similar to survival following surgical bypass[32] and supports the case for further controlled studies.

Table 1 *Characteristics that affect selection of an unsealed source*

Cytotoxic range, advantage of 'field effect'
Type of radiation
Energy characteristics
Half-life, therapeutic effects and logistical problems
Biodistribution
Cost and availability
Ease of synthesis/conjugation to suitable vehicle

Unsealed sources

The features which should be considered when selecting an isotope for use as an unsealed source are summarized in *Table 1*.

The cytotoxic range of the isotope is a reflection of the relative activities of the types of radiation produced. Cytotoxic range is thus determined by the type of radiation (α, β, or γ) produced and the energy characteristics of each type Isotopes with a greater range, such as yttrium-90, irradiate a greater volume of tissue and thus exhibit a 'field effect' which may compensate for irregular distribution of the isotope within tumour tissue.

The physical half-life of the isotope determines the cumulative radiation dose to adjacent tissues and is also an important determinant of potential hazards, both to the patient and to hospital staff. Isotopes with a long half-life pose proportionally greater logistical problems in terms of radiation protection. Patient isolation in shielded rooms, facilities for disposal of radioactive waste, special arrangements for transport to and from hospital, and monitoring of staff exposures may be necessary.

The biological fate of isotopes varies considerably. Iodine-131 is actively excreted in body fluids, whereas yttrium-90 is retained within the body indefinitely. Isotopes with high excretion rates will have a physiological half-life which is much shorter than the physical half-life. Significant excretion in body fluids may cause additional radiation protection problems, particularly in sick or elderly patients.

Iodine-131 is in some respects the ideal unsealed therapeutic isotope, as its decay produces both β and γ radiation. β particles have a penetration of only a few millimetres and thus have a potent localized tumoricidal effect; they are not detectable by external scintigraphy. The absorption of γ radiation by body tissues is, however, incomplete, allowing accurate dosimetry measurements to be made using external scintigraphy. Iodine-131 has a relatively low β energy of 600 keV and a cytotoxic range of only 2 mm. The physical half-life is just over 8 days, although the biological half-life is nearer 5 days as a result of excretion in urine and saliva. Thyroid uptake is a potential problem, but is easily prevented by pre-treatment with potassium iodide.

Unlike iodine-131, yttrium-90 is a pure β-emitter with a much greater maximum β energy of 2·27 meV and a greater cytotoxic range of 11 mm. The mean penetration in tissues is 2·5 mm, or roughly 100–1000 cell diameters. The physical half-life of yttrium-90 is considerably shorter than that of iodine-131 at 64 h. The advantages of yttrium-90 over iodine-131 may be summarized as follows: (1) no γ'emission, obviating the need for patient isolation; (2) a greater tumour radiation dose per mCi of isotope; (3) a greater tumour dose rate; and (4) a larger field of irradiation (cytotoxic range).

Against these must be set two major disadvantages: (1) catabolized yttrium is not excreted, but is concentrated in the liver, spleen and bone, resulting in a dose-related risk of marrow suppression; and (2) biodistribution, in particular bone absorption, cannot be measured by external imaging owing to the lack of γ emission.

Routes and methods of administration

Unsealed radio-isotope sources may be administered directly into the tumour or embolically via the hepatic artery in the form of microspheres or lipid droplets. Less invasive and more elegant, isotopes attached to tumour-specific antibodies can be given via parenteral infusion.

Direct intratumoral injection

Injection of yttrium-90 microspheres into tumours raised in an animal model has been reported to result in a significant reduction in tumour size and prolonged survival in the treated group[33]. No results have been reported in human subjects to date.

Regional infusion

In its simplest form, site-specificity can be achieved by merely infusing the isotope into the vascular supply of the organ or tumour itself. Most tumours receive their blood supply largely from the hepatic artery, and further selective localization of the isotope within tumour results from increased blood flow through the tumour neovasculature. This might be considered a form of mechanical targeting. Persistent localization within tumour requires a method of 'fixing' the isotope, most commonly by the deposition of microemboli.

Yttrium-90 resin or ceramic microspheres have been investigated in regional radiotherapy of the liver, both alone[34,35] and experimentally in combination with the radiosensitizer 5-bromo-2'-deoxyuridine (BUDR)[36]. Microspheres incorporating stable yttrium-89 are converted to yttrium-90 by bombardment with neutrons in a nuclear reactor. The usefulness of yttrium microspheres as a therapeutic modality has been limited thus far by two major side-effects Leaching of yttrium-90 from the resin or ceramic matrix has occurred, with accumulation of the isotope in bone, leading to myelosuppression and death[37]. In addition, the embolic effect of infusing microspheres commonly results in shunting of the spheres into other visceral branches and the systemic circulation, resulting in gastrointestinal bleeds and pulmonary fibrosis. Newer glass microspheres (Theraspheres, Theragenics, Atlanta, USA) have overcome the problem of leaching, and are reported to be non-toxic in animal experiments[38], with no liver damage or myelosuppression despite doses of up to 300 Gy. Preliminary clinical studies in HCC and metastatic tumours[24,39,40] have achieved tumour:liver dose ratios of around 6:1. Assuming a uniform distribution of the microspheres, the authors estimate a radiation dose of 4·92 cGy per kg of liver for each MBq of yttrium administered. No significant toxicity was seen in seven patients with HCC, but neither was any measurable tumour response observed. Plastic microspheres have also been evaluated, with reduction in tumour size in seven of 16 patients with liver metastases[41]; however, gastrointestinal bleeding due to shunting of the microspheres remains a problem. Houle *et al.*[24] suggest preassessment of potential shunts using technetium-99-labelled-human albumin microspheres: measurement of activity in the lungs, liver and stomach allowing calculation of a 'shunt fraction'. Burton *et al.*[42,43] advocate the use of an intraoperative β-detection probe to scan and assess radiation dosage to tumour and normal tissues.

The size of microsphere employed determines the degree of tumour selectively: spheres up to 32 μ in diameter produce a tumour:liver ratio of 3·1, whereas above 50 μ the ratio is unity[44]. Theraspheres are 15–30 μ in diameter (mean 20 μ)

Lipiodol

Lipiodol (May and Baker, Reading, UK) is a stable iodine addition product of fatty acid ethyl esters derived from poppyseed oil: it contains 475 mg of iodine per ml (38 per cent by weight) and has been used for many years as a lymphographic contrast medium. In 1979 it was observed that when Lipiodol was infused into the hepatic artery, selective retention of the oil was seen in foci of hepatocellular carcinoma[45]. Lipiodol has been used in this way for clinical localization studies and has been found to be particularly effective in demonstrating the small 'daughter' nodules often found in association with the main tumour mass of HCC[46]. Several uncontrolled series have reported increased survival in patients with HCC using intrahepatic arterial infusion of Lipiodol in combination with various cytotoxic agents, including doxorubicin, its derivative epirubicin, and mitomycin C[47–49].

Patterns of Lipiodol accumulation in liver tumour tissue vary with respect to the tumour type. Diffuse homogeneous uptake is seen in HCC, deposits of which are frequently hypervascular. Peripheral uptake with a central defect is usually seen in colorectal liver metastases which commonly exhibit a rim of dilated peritumoral sinusoids around a relatively avascular centre. These findings would tend to support the theory that Lipiodol retention in the initial phase is due to microvascular entrapment. Studies of the biodistribution of iodine-131-labelled-Lipiodol have shown marked activity in the spleen, bone marrow and lungs. This may also represent deposition of microvascular lipid emboli, or may be due to uptake by the reticuloendothelial system[50]. Recent histological studies have attempted to elucidate the long-term fate of Lipiodol, and have demonstrated both cellular uptake and membrane adhesion of lipid droplets by tumour cells[51]

The selective retention of Lipiodol by hepatic tumour tissue makes it an ideal vehicle for the delivery of internal radiotherapy. A fraction of the iodine component can be replaced, using a simple exchange reaction, by iodine-131. Distribution of the radiolabelled lipid has been studied using scintigraphy and shows a similar preferential uptake and retention in tumour tissue to non-radioactive Lipiodol[52]. In an animal tumour model it has been shown to have a significantly longer effective half-life in tumour than in normal tissue and has resulted in almost complete necrosis of the tumour[53]. Early reports from clinical trials of patients with HCC have also been encouraging, with reduction of both tumour size and ascites, and symptomatic improvement in most cases. Tumour:non-tumour ratios of up to 20:1 have been achieved, and toxicity to surrounding liver parenchyma, bone marrow and lung has not been reported[54–56]. In small foci of hepatocellular carcinoma it appears capable of complete tumour ablation[57]. Initial studies have shown selective retention in small colorectal metastases, but localization in larger deposits is very poor[58]

Despite the ease of synthesis of iodine-131-labelled-Lipiodol, it has been suggested that iodine-131 may not be the best isotope for targeted hepatic radiotherapy. Park *et al.*[54] have proposed yttrium-90 as a more suitable isotope in theory, based on its greater β energy and range, arguing that the increased range would compensate for the effects of uneven lipid distribution within the tumour. While the increased energy and range of yttrium-90 might be advantageous in the case of a large, relatively avascular tumour, its uptake in therapeutic amounts by multiple smaller deposits might result in the delivery of an unacceptable radiation dose to the surrounding normal tissue, thus defeating the object of targeted therapy. No experimental or clinical data are presently available on the use of yttrium-90-labelled-Lipiodol.

Antibody-guided targeting of hepatic tumours

Antibody localization by tumours was first reported by Pressman and Korngold in 1953[59], who demonstrated superior localization within tumour of antibodies raised against a sarcoma when compared to non-immune serum. The discovery of the tumour-associated serum proteins alphafetoprotein, carcinoembryonic antigen and beta-human chorionic gonadotrophin in the 1960s spurred further studies into the role of tumour antigen–antibody binding, and this concept was enhanced by the development of monoclonal antibodies in the mid-1970s. Monoclonal antibodies are pure isolates of single antibodies raised against specific tumour antigens. In theory they should not recognize other targets and should therefore be the ideal method of targeting radio-isotopes to tumours.

Initial attempts at producing monoclonal antibodies to primary hepatocellular carcinoma were encouraging. Scintigraphy obtained after intravenous administration of radiolabelled antibody showed excellent tumour localization, including images of extrahepatic spread of disease[60]. However, autoradiography of tissues thus treated showed patchy localization of the isotope. This uneven localization probably resulted from four distinct biochemical and biophysical factors: (1) a variation in blood supply to different regions of the tumour; (2) binding of monoclonal antibodies to secreted antigens in the extracellular space; (3) heterogenicity of antigen expression by the tumour; and (4) cross-reactivity with antigens expressed on the surface of cirrhotic cells[60]. This lack of true tumour specificity continues to present a major obstacle to successful targeting.

The solution would seem to lie in the identification of antigens which are expressed by tumour cells and no others. To date, however, most antigens studied have proved to be tumour-associated rather than truly tumour-specific. HCC cells have been shown to have a high concentration of ferritin[61], and work with polyclonal anti-ferritin antibodies has produced the most impressive results in clinical trials. Order *et al.*[62] have treated 105 patients using a multimodal regime including polyclonal iodine-131-labelled-anti-ferritin, and report improved response rates and survival. Further work from their unit described seven patients with hepatocellular tumours considered unresectable on the grounds of size, spread or location who were treated with the same antibody complex, and whose tumours shrunk to a size where they could be successfully resected[63]. The same group has also reported good results in unresectable intrahepatic cholangiocarcinoma[64], with partial remission periods of up to 4 years. However, since their treatment protocol also includes external beam radiation and systemic chemotherapy with doxorubicin and 5-fluorouracil, it is difficult to assess the contribution of iodine-131-labelled-anti-ferritin to their results.

Yttrium-90 offers theoretical advantages over iodine-131 in delivering higher dose rates and greater total doses to the targeted tumour. Initial studies of yttrium-90-labelled-anti-ferritin IgG in hepatoma suggest that toxicity to bone marrow remains the major dose-limiting factor. Order *et al.*[65] have reported a series of 13 patients, all but two of whom sustained marrow toxicity despite a median tumour dose of only 1800 cGy. Cross-reactivity with the immunologically similar ferritin in non-neoplastic liver, heart and spleen remains a problem. Biodistribution cannot be accurately determined by external imaging techniques, although the same unit has reported the distribution to be similar to that of iodine-131-labelled-anti-ferritin[66]. Preassessment with indium-111-labelled-anti-ferritin has been suggested as a means of evaluating tumour uptake. The logical extension of this work is to use monoclonal anti-ferritin, and provisional reports have shown improved tumour dose deposition in an animal model[67].

Good localization of iodine-131-labelled-anti-carcinoembryonic antigen monoclonal antibody has been reported in colorectal metastases[68], but the delivery of a lethal radiation dose to tumour cells is not yet within the scope of monoclonal techniques. This is due to the low levels of tumour uptake currently achievable, 'energy wastage' resulting from targeting microscopic deposits with an isotope whose disintegration energy is widely dissipated, and host reaction to the antibody. Wheldon *et al.*[69] have proposed a theoretical strategy for maximizing the effectiveness of treatment to small metastases, between 1 mm and 10 mm in diameter. They suggest combining the selective qualities of antibody-targeted isotope therapy with total body irradiation, with the use of appropriate protecting screening to reduce the total dose to organs which retain the complexes (i.e. liver, spleen and lung).

Host reaction to the injected antibody remains the major adverse effect of monoclonal antibodies. This may range from acute hypersensitivity to failure of the treatment because of the formation of immune complexes. These effects may be reduced by using antibody fragments, which lack the antigenic Fc portion, or by inducing tolerance using anti-T cell antibodies or cyclosporine A. Development of monoclonal antibodies raised in humans may avoid the problems of host reaction[70].

Side-effects and dosimetry

The therapeutic ratio of a treatment represents the maximum tolerated dose divided by the minimum effective dose. Increasing the amount of isotope administered may increase the total tumour dose but not the therapeutic ratio. Accurate estimation of the radiation doses to tumour, hepatic parenchyma and other organs is therefore necessary Two methods are in use. First, calculation using medical internal radiation dose (MIRD) standard tables, using information on tumour volume from CT or MRI scans, and on cumulated activity in tumour and other tissues from serial scintigraphy[71]. The accuracy of planar imaging depends on the tumour:liver dose ratio achievable, and overestimation is common with monoclonal antibodies because of activity in overlying and underlying tissues. A major advantage of iodine-131-labelled-Lipiodol over iodine-131-labelled-monoclonals is its near complete elimination from non-neoplastic hepatic parenchyma within 10 days. The lack of γ emission from surrounding tissues allows more accurate estimates of tumour dose using simple planar imaging techniques[72,73]. Second, single photon emission tomography (SPET) provides three-dimensional data, permitting exclusion of the activity from surrounding tissues. Compton scatter (the production of secondary electrons within the target tissue) remains a source of inaccuracy, but can be corrected for using a sophisticated scatter correction algorithm[74].

Systemic effects of high doses of radio-isotopes include radiation hepatitis and pulmonary fibrosis. In practice, however, the dose of isotope administered is limited by bone marrow suppression, which is proportional to the rate of clearance from blood. Clearance may be accelerated to improve the therapeutic ratio, e.g. by injecting a second antibody raised against a monoclonal after 24 h. Toxic effects may also be blocked; potential thyroid damage with iodine-131 can be prevented by pre-treatment with potassium iodide and potassium perchlorate.

Conclusions

Liver tumours represent a major cause of mortality throughout the world; only a small percentage of cases are amenable to surgery, and without it the prognosis is very poor. The use of isotopes for internal radiotherapy of tumours is not a new concept, but none the less one which has been largely ignored in the liver thus far. Major advances in radiopharmaceutical techniques over the past 5 years have resulted in improved methods of delivery and therapeutic ratios. As a sealed source, iridium-192 wires in combination with internal stenting have been shown, at least in uncontrolled studies, to palliate malignant biliary strictures as effectively as bypass surgery. Iodine-131 is a safe unsealed source which can be selectively delivered to tumour foci, although only iodine-131-labelled-Lipiodol is at present capable of delivering a potentially tumoricidal dose. Yttrium-90, undoubtedly the most powerful isotope currently available, remains too dose-limited by its lethal side-effects to possess widespread therapeutic applications. In addition to controlled trials of radiotherapeutic techniques, a more detailed understanding of tumour biology is necessary if radio-isotopes are to be exploited to maximum effect in the treatment of hepatobiliary malignancy.

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Review

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Gynaecomastia

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This paper reviews the development of excess breast tissue in the male. Gynaecomastia is a common problem and may have a physiological or pathological basis. It can be dealt with in most cases by reassurance or simple surgery.

The development of excess breast tissue in the male is a common phenomenon It is a source of embarrassment to the adolescent and of surprise and concern to the older male. There may be a physiological or a pathological basis to it (*Table 1*) but, as far as the surgeon is concerned, gynaecomastia has two important aspects First, the distinction between breast development purely because of physiological disturbance and that owing to a pathological basis must be made. In older men in particular, a breast tumour may also have to be excluded Second, it is occasionally necessary to correct the cosmetic deformity.

Between 10 and 20 cases of gynaecomastia are seen each year in the average general surgical outpatient department How necessary is it to seek an underlying pathological cause? How aggressively should the patient be investigated and how likely is an abnormality to be detected? When considering treatment of the breast itself, either because of cosmetic considerations or local discomfort, is surgery indicated or is medical treatment available? If medical treatment fails to relieve the problem, how should gynaecomastia be managed surgically?

Many males experience physiological gynaecomastia at some stage in their life; in addition to physiological disturbances there are many pathological stimuli to breast development such as drugs, tumours, liver and renal failure, and hormonal abnormalities Whatever the aetiology, the ultimate cause of gynaecomastia is an increase in the effective oestrogen: testosterone ratio. This is usually due to an alteration in serum levels[1,2], but in some cases these changes may only occur at tissue level because of local enzyme activity in the breast[3] Alternatively, there may be a selective change in breast tissue sensitivity to one or other hormone[4].

Macroscopic and microscopic appearance

Gynaecomastia usually presents as a firm disc of tissue underlying the nipple. In most cases it is bilateral, although in some patients breast development occurs on one side months before bilateral development becomes apparent. Only about 10 per cent of cases are truly unilateral[5]. The criteria for diagnosis vary; most authorities require the existence of a disc of breast tissue at least 2 cm in diameter[5–7], although others have made the diagnosis when only 0·5 cm of breast tissue is present[8].

The microscopic appearance depends on the duration of development. In the early stages there are prominent ductules in loose connective tissue, but with time these are replaced to dense hyalinized fibrous tissue[9]

Simon *et al.*[10] graded gynaecomastia on the basis of size (*Table 2*).

Physiological gynaecomastia (*Figure 1*)

Gynaecomastia is rare before puberty except for its transitory appearance in the neonate However, at puberty 30–65 per cent of boys have some breast development, which lasts only a few months in the majority of individuals. In almost 75 per cent of boys, breast development subsides within 2 years and in less than 8 per cent does it exist for more than 3 years[8] During middle age, about 30 per cent of men develop gynaecomastia with no obvious pathological cause[9–11], and its prevalence gradually increases to over 60 per cent in the seventh decade[10,12]

The neonatal breast is influenced by maternal oestrogens, but these soon disappear and breast development subsides At puberty there is a sudden surge of pituitary gonadotrophins Luteinizing hormone stimulates the Leydig cells of the testis to secrete both oestrogen and testosterone In the adult male, more testosterone is produced, but at puberty oestrogen production is

Table 1 *Major causes of gynaecomastia*

Physiological	Metabolic
Neonate	Cirrhosis
Puberty	Hyperthyroidism
Ageing	Renal failure/dialysis
Drugs	Starvation/re-feeding
Tumours	Hypogonadism
Testis	Viral
Bronchus	Trauma
	Maldescent
	Chromosomal

Table 2 *Classification of gynaecomastia* (*Simon* et al [10])

Grade 1	Small but visible breast development with no redundant skin
Grade 2a	Moderate breast development with no redundant skin
Grade 2b	Moderate breast development with redundant skin
Grade 3	Marked breast development with much redundant skin

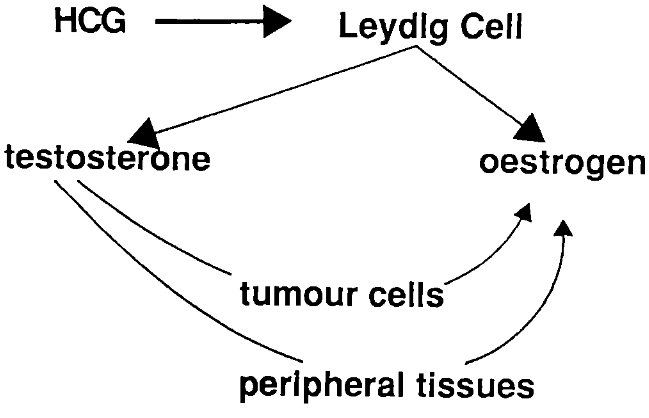

Figure 1 *Oestrogen and androgen production in men*

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thought to reach adult levels before testosterone and this results in a transitory rise in the oestrogen:testosterone ratio[13–15]. The testis is not the only source of oestrogens. The adrenal glands produce small quantities of weak androgens, most of which are metabolized by the liver. Excess androgens, however, are 'aromatized' to oestrogens in the peripheral tissues, especially fat In a prospective study of young boys studied through puberty, Moore *et al.*[4] found that adrenal androgen levels were lower in those boys who subsequently developed gynaecomastia, and they suggested that prepubertal hormones influenced the sensitivity of breast tissue to oestrogens at puberty.

Several studies have addressed the possibility of other local hormonal variations which might predispose to gynaecomastia. Oestrogen and androgen receptor status have been intensively studied in the readily available specimens of gynaecomastia and breast carcinoma but, unfortunately, not in normal male breast tissue. Reports of tissue positivity vary from 10 to 90 per cent for oestrogen receptors and 20 to 75 per cent for androgen receptors[16–18]. In general, tissue from gynaecomastia is less likely to have oestrogen receptors than is male breast carcinoma, but no comparison with normal male breast tissue is available. Levels of aromatase activity appear to vary among individuals and there are cases of familial gynaecomastia associated with high aromatase activity in peripheral tissues, including the breast[19].

Testicular function declines with increasing age; testosterone production is affected relatively more than that of oestrogen. In addition, weight often increases with age and at least one study[10] has demonstrated a significant association between obesity and gynaecomastia. This is the result of increased capacity for conversion of adrenal and testicular androgens to oestrogen by aromatases in fat The same study found that gynaecomastia was less common in men over 70 years because of reduction in average body weight.

Pathological gynaecomastia

Drugs

Drugs are the most common cause of 'pathological' breast development, especially in men over 50 years, and accounted for 62 per cent of cases in one hospital-based study of veterans[11].

A vast range of drugs have been held responsible for gynaecomastia. Oestrogens, usually given for carcinoma of the prostate, are a frequent cause. Less commonly, unprescribed oestrogens are to blame, e g those absorbed through the skin from industrial use[20] or vaginal cream from the sexual partner[5] Other drugs, such as digitalis[21], may have an oestrogenic effect. Some drugs have an anti-androgen effect, cimetidine has long been associated with gynaecomastia for this reason but usually only when used in high dose[22,23]. The same effect has not been seen with ranitidine

The mechanism of action for most drugs associated with gynaecomastia is unclear. Spironolactone[24], methyldopa[11], captopril[25] and calcium channel blockers[26] have also been associated with breast enlargement. Anti-fungal agents such as ketoconazole, in prolonged high dosage, have also been linked with gynaecomastia[27]. Tricyclic anti-depressants[11] and diazepam[11] have also been implicated

Chemotherapeutic agents and radiotherapy can cause gynaecomastia, especially in patients who have had an orchidectomy for testicular cancer[28,29]. Testicular function is already reduced and further suppression of the remaining testis by treatment may alter the oestrogen.testosterone ratio This can lead to worries about recurrent tumour causing gynaecomastia (see below), but if breast development is because of treatment rather than tumour, the prognosis is said to be good[30]. Such gynaecomastia usually develops 2–9 months after treatment and resolves within a few months. Gynaecomastia has also occasionally been described in association with radiotherapy or chemotherapy for other conditions such as Hodgkin's disease[31].

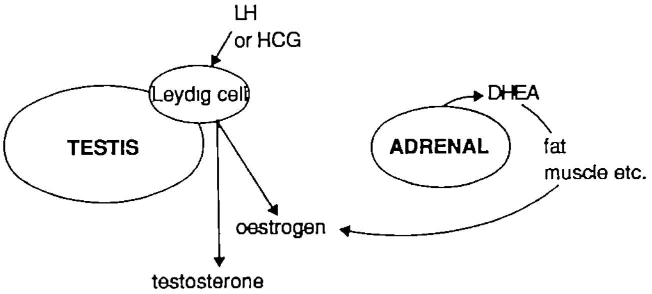

Figure 2 *Oestrogen and testosterone production associated with malignant testicular tumours. DHEA, dehydroepiandrosterone*

Drug abuse may lead to gynaecomastia. Marijuana and heroin are well described causes[32,33].

Testicular tumours (Figure 2)

These are an equally important though less common cause of gynaecomastia. Gynaecomastia may be an early manifestation and may appear before the tumour is palpable[34]

Benign Leydig cell tumours cause gynaecomastia if they produce an abnormally high amount of oestrogen relative to testosterone. These tumours are rare but 30 per cent are associated with breast development[35].

The most common testicular tumours causing gynaecomastia are those producing chorionic gonadotrophin (HCG)[36]. This hormone stimulates Leydig cells to produce both testosterone and oestrogen, testosterone is converted to oestrogen not only by peripheral tissues but also by the tumour itself[37]. Up to 10 per cent of malignant testicular tumours cause gynaecomastia[28], and are said to have a worse prognosis[28,36] than those that do not.

HCG production varies with tumour type. It is found in all chorionic carcinomas, in 58 per cent of embryonal tumours but in only 38 per cent of seminomas[38]. However, relatively few tumours that produce HCG are associated with gynaecomastia. Thus, breast development occurs in 10–20 per cent of chorionic carcinomas[39], in 4 per cent of embryonal tumours[40] and in only 1 per cent of seminomas[40].

Other tumours

These usually induce gynaecomastia via HCG production[41]. The most common such tumour is the bronchial carcinoma, but occasionally gastric or pancreatic malignancies act in this way Adrenal tumours may cause gynaecomastia because of excessive production of adrenal androgens which are then converted to oestrogen. Hepatic tumours have been described in association with breast development, the mechanism is thought to be increased aromatase activity in the tumour itself[42].

Hepatic cirrhosis

This is an important cause of gynaecomastia. It is thought to involve reduced liver clearance of adrenal androgens so that more are available for conversion to oestrogens in the periphery[43,44].

Hyperthyroidism

Between 10 and 40 per cent of men with thyrotoxicosis have gynaecomastia[45]. The cause may be both increased adrenal androgen production and greater peripheral aromatization of androgens to oestrogen[46].

Re-feeding after starvation

Breast development is common in prisoners-of-war[47]. During starvation, gonadal function is suppressed and this in itself may be associated with gynaecomastia. More commonly, however, it is re-feeding, leading to re-activation of the pituitary adrenal axis and renewed stimulation of the testis, that produces gynaecomastia, in much the same way as at puberty

Renal failure and dialysis

This mechanism resembles that of re-feeding after starvation. Testicular function is suppressed in renal failure but recovers on dialysis Thirty per cent of patients undergoing dialysis develop gynaecomastia between 4 weeks and several months after starting treatment, but symptoms usually resolve within a year[48,49].

Hypogonadism

Primary failure of the testes to produce adequate testosterone leads to increased levels of pituitary gonadotrophins. High gonadotrophin levels stimulate a relative excess of oestrogen secretion from the flagging testes[50], which may lead to gynaecomastia. There are many causes of testicular failure leading to gynaecomastia, both physiological (ageing) and pathological. Chromosomal aberrations responsible include Klinefelter's disease in which 40 per cent of patients develop gynaecomastia at puberty[51–53]. Congenital enzyme defects may prevent androgen production. Other, more common, causes are congenital abnormalities of maldescended testes, and traumatic or viral damage, such as mumps[54]

In some circumstances, the pituitary testicular axis is suppressed as in renal failure, starvation and alcoholism. Absolute levels of testosterone are reduced but oestrogens are still produced by conversion of adrenal and testicular androgens, thus disturbing the oestrogen·testosterone ratio. In testicular feminization syndrome, the breast tissue is insensitive to the effects of testosterone and this increases the effective oestrogen:testosterone ratio.

Other causes

In addition to bronchial neoplasms, other chronic lung diseases associated with hypertrophic osteoarthropathy, such as tuberculosis and cystic fibrosis, have been thought to cause gynaecomastia, but the mechanism is unclear[55].

Breast development is occasionally associated with periods of anxiety[56] owing to suppression of the pituitary–testicular axis It has also been described in HIV infection: the virus is similar to that causing mammary hyperplasia in sheep but the mechanism is not known[57]

Differential diagnosis

Unilateral breast swelling should not be assumed to be gynaecomastia unless carcinoma of the breast has been excluded. Asymmetry in relation to the nipple, undue firmness or fixation, ulceration or the presence of palpable axillary nodes should always raise suspicion Mammography and ultrasonography have both been used to investigate the male breast[58,59], but fine needle aspiration cytology is probably the investigation of choice if doubt exists[60]· if this fails to prove the diagnosis, then the breast should be biopsied

Carcinoma of the male breast is rare (less than 1 per cent of all male malignancies) It is relatively common in Klinefelter's syndrome[61], and is seen in other circumstances where gynaecomastia is sometimes found There seems to be a common hormonal basis to these two conditions, but there is no evidence that gynaecomastia predisposes to carcinoma of the breast[62]

Another condition to be considered in the differential diagnosis is pseudogynaecomastia owing to fat deposition on the chest The difference is usually obvious on palpation the tissue feels much softer and ill-defined than the firm disc of tissue associated with true gynaecomastia.

Who and how to investigate

Apart from the neonate, breast development in prepubertal boys always has a pathological basis[63] If pubertal boys with gynaecomastia have concordant growth indices, then there is probably little point in any investigation In the remaining patients, approximately half will have an abnormality responsible for gynaecomastia[54]. In this group a thorough review of the drug history is obviously important. Clues to thyroid status and liver function should be sought in the history and examination, and the testes examined for evidence of tumour or atrophy. Even if the latter appear normal, ultrasound examination should be performed to exclude a small neoplasm[64,65]. A chest X-ray is mandatory, but skull X-ray and prolactin levels are usually unhelpful and unnecessary. Serum HCG, luteinizing hormone, oestrogen and testosterone levels should be measured, and thyroid and liver function investigated[11,63]

Treatment

In most cases of physiological gynaecomastia, reassurance is all that is needed In those adolescents severely embarrassed by breast development, psychological factors may dictate the need for more active intervention Treatment of any underlying disease is of paramount importance, but this may fail to resolve the breast development, especially if it has been present for some time, and further treatment may be necessary

Drug-induced gynaecomastia may be treated by simply stopping the offending medication If this is not possible, reassurance with review is necessary.

Hormonal treatment

In theory, correction of the effective oestrogen testosterone ratio should lead to resolution of the gynaecomastia Trials of such treatment are, in general, small and poorly controlled Adequate controls are important when investigating a condition which often resolves spontaneously.

Attempts to increase androgen levels by giving exogenous androgen tend to be frustrated by its conversion to oestrogens, although in cases of profound deficiency androgens are often helpful[54] Non-aromatizable androgens, such as dihydrotestosterone, have been developed to circumvent the problem of conversion[66] Another method is inhibition of the aromatization of naturally occurring androgens by administering testolactone, thus reducing the production of oestrogens[67].

Anti-oestrogens have been tried. Clomiphene proved unsuccessful and was associated with adverse side-effects[68] However, in a controlled trial, tamoxifen has been shown to reduce gynaecomastia successfully in 70 per cent of middle-aged men[69], and has also proved useful in pubertal gynaecomastia[70] More recently, danazol has also been shown to be effective in reducing both the pain and extent of gynaecomastia[71]

Surgical treatment

Surgical correction of gynaecomastia was described in the 16th century by Paulus Aeginata The original approach to gynaecomastia was simple mastectomy[72], but the linear scar and lack of nipple made this unacceptable for what was essentially a cosmetic problem Most gynaecomastia is classified as grade 1 or 2a and can be dealt with by a subcutaneous mastectomy through a peri-areolar incision, usually along the inferior half of the areola[73]. Even this can lead to unsatisfactory results because of difficulties in leaving a smooth contour to the chest outline rather than producing a crater in which sits the nipple This tendency to produce an unsightly crater can be reduced by leaving a disc of breast tissue beneath the nipple, thus in reality performing a subtotal subcutaneous mastectomy. If there is redundant skin it may improve spontaneously by postoperative shrinkage, but in some grade 2b gynaecomastia and certainly grade 3, excess skin has to be removed to restore the contour of the breast and prevent nipple sagging. In addition, access to remove breast tissue must be adequate and the nipple must be preserved. All these requirements have to be fulfilled with minimal scarring. Various techniques have been devised, such as excising an ellipse from the areolar margin[74] or undertaking simple mastectomy with free nipple graft[75]. More recently, plastic surgical techniques that preserve the areolar blood supply have been advocated[76–78]. Saad and Kay[77] recommend removal of excessive breast tissue via a circumareolar incision which preserves the dermal vascular plexus to the nipple. This approach also has the advantage that the diameter of the incision can be made to correspond to the size of the normal contralateral areola, thus improving the cosmetic appearance. Ward and Khalid[78] recommend that, for grade 3 gynaecomastia, the excess tissue is removed through a horizontal elliptical incision similar to that employed for breast reduction. The medial and lateral triangles of skin, along with underlying fat and breast tissue, are excised, leaving a vertical bipedicle flap which allows vascular perfusion of the nipple and a good cosmetic result.

A recent development is liposuction[79], but, although it may prove a useful adjunct to excision of breast tissue to leave a smoother outline[80], it cannot deal entirely with true gynaecomastia because it removes fat rather than breast tissue.

Conclusion

Gynaecomastia is a common problem which can be dealt with in most cases, certainly those which develop around puberty, by reassurance or simple surgery. After puberty, although many cases are idiopathic or physiological, underlying disease should be excluded Up to early middle age, a testicular tumour must be excluded by ultrasound examination even if clinical examination is normal Beyond this age, drugs are commonly to blame, but bronchial carcinoma, liver cirrhosis or thyrotoxicosis should be considered.

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Limitations of surgery in the treatment of retroperitoneal sarcoma

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A retrospective analysis was undertaken of 120 patients with retroperitoneal sarcoma referred to the Royal Marsden Hospital over a period of 20 years. The actuarial 5-year survival rate of all cases following referral was 29 per cent. On univariate and multivariate analysis the principal factors associated with an unfavourable prognosis were the presence of metastases, poor performance status at presentation, high tumour grade and incomplete excision of the primary tumour. The single most important factor affecting the ability to remove the primary tumour completely was multiple organ involvement. After apparently complete excision, however, the probability of local recurrence by 5 years was 85 per cent (95 per cent confidence interval 56–99). The prognosis of patients with retroperitoneal sarcoma is poor.

The prognosis of patients with retroperitoneal sarcoma is poor, with an overall 5-year survival rate of 12 to 40 per cent[1–8]. The most favourable prognosis is achieved by complete excision of the primary tumour but the proportion of patients in whom this is accomplished is less than 50 per cent and local recurrence is common[1–10]. Failure to accomplish complete excision is attributed to a number of factors: the size of the tumour, its location and the number of organs involved[2,3]. The relative importance of these factors has not been specifically examined. A retrospective study of 120 patients with retroperitoneal sarcoma referred to the Soft Tissue Sarcoma Unit at the Royal Marsden Hospital was therefore undertaken to determine the principal factors affecting resectability, their relationship to overall survival and the risk of local recurrence

Patients and methods

Between 1970 and 1990, 120 patients with primary retroperitoneal sarcoma were referred for treatment to the Royal Marsden Hospital. A comprehensive database was created in 1986 from which the present retrospective study was compiled

Specimens were reviewed and tumours classified according to the WHO classification of soft tissue tumours[11] and assigned to one of three grades. Immunohistochemical techniques and electron microscopy were used when tissue samples were available[12] In some cases grade was determined by the diagnosis; for example, rhabdomyosarcoma was invariably considered to be high grade, in others it was determined from the extent of necrosis, mitotic index, cellularity, pleomorphism and the degree of differentiation[13] Tumours were staged according to the conventions of the International Union Against Cancer (UICC)[14], but poorly differentiated (G3) and undifferentiated tumours (G4) were grouped together.

Surgical excision was defined as complete when the tumour was resected without breaching its capsule. Other procedures, including palliative debulking, were defined as incomplete. Performance status was evaluated using the WHO system in which patient activity is scored from 0 to 4, 0 representing normal activity and 4 representing complete disability[15].

A few patients with inoperable disease received radiotherapy as the only treatment. In others, radiotherapy was given selectively depending upon the grade of the tumour, its location and the completeness of surgical excision The aim was to deliver 60 Gy to the tumour bed, having planned treatment using computed tomography (CT)

Patients given chemotherapy for metastatic, inoperable or gross residual disease were randomized to receive courses of either doxorubicin (1 62 g/m^2) or ifosfamide (60 mg/m^2) at 3-weekly intervals A patient crossed over to the alternative regimen on relapse or with evidence of disease progression, no response or partial response, after two, four and nine courses of treatment respectively

Since 1984, abdominal and pulmonary CT scanning was undertaken on all patients referred with retroperitoneal sarcoma. After treatment patients were followed when possible at 3-monthly intervals for 1 year, 6-monthly intervals for the next near and annually thereafter A chest radiograph was performed at each attendance, and abdominal and/or pulmonary CT scans were undertaken if recurrence was suspected on clinical grounds

The probability of achieving complete excision was analysed by stepwise logistic regression. The model fitting the observed data best was calculated by computer. The following variables were examined: age, sex, maximum tumour diameter, tumour grade, tumour subtype, number of organs involved, principal organs involved, previous surgery, previous chemotherapy and previous radiotherapy

Survival and recurrence rates were calculated by the Kaplan–Meier method, and univariate comparisons were performed with the log rank test and the log rank test for trend[16] The following additional variables were included in a multivariate analysis of survival using Cox's proportional hazards model (BMDP Statistical Software Inc., UCLA): performance status, extent of surgery (complete *versus* incomplete excision) and the presence of metastases at presentation to the Royal Marsden Hospital. Missing values were included as a separate covariate.

Survival was measured from the time of referral to the Royal Marsden Hospital[17] .In the analysis of survival, surgical procedures performed before referral were classified as previous surgical events and not distinguished according to the completeness of excision

Details of other statistical tests are provided in the text. Results were taken to be significant at the 5 per cent level, and 95 per cent confidence intervals are given in parentheses where appropriate

Results

Clinical characteristics

Seventy-five of the 120 patients (63 per cent) were referred with tumours which had not been previously explored Forty-five (38 per cent) had recurrent or residual disease following surgery elsewhere. The median age of patients at presentation was 50 years (range 1–75). The male:female ratio was unity (*Figure 1*).

The most common presenting symptoms among the 107 patients with details were an abdominal mass (59 per cent) and pain (48 per cent) Weight loss was reported in 15 per cent of cases. The median duration of symptoms before presentation was 2 months (range < 1–37). An abdominal mass was palpable in 101 patients (84 per cent) at the time of referral.

Performance status on referral was evaluable in 100 patients: 18 were judged to be in category 0, 68 in 1, and 14 in categories 2–4.

Histopathology and stage

The distribution of tumours according to the histopathological

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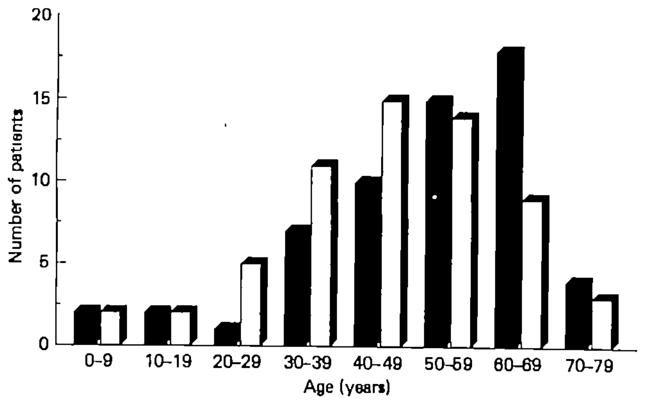

Figure 1 *Age and sex distribution of 120 patients with retroperitoneal sarcoma* ■, *Male,* □, *female*

Table 1 *Histology of 120 retroperitoneal sarcomas*

Sarcoma type	Number of cases
Leiomyosarcoma	40 (33)
Malignant fibrous histiocytoma	30 (25)
Liposarcoma	23 (19)
Rhabdomyosarcoma	7 (6)
Malignant nerve sheath tumour	6 (5)
Fibrosarcoma	4 (3)
Synovial sarcoma	1 (1)
Sarcoma NOS	9 (8)

Numbers in parentheses are percentages

diagnosis is given in *Table 1*. Among 83 cases in whom clinical size was specifically recorded, 75 had tumours greater than 5 cm in diameter. The median (maximum) diameter was 15 cm (range 1–46). Forty-six (38 per cent) tumours were low grade, 16 (13 per cent) were intermediate grade and 52 (43 per cent) were high grade. No grade was assigned in six cases

Metastases were present in 20 patients at original presentation, and, on referral, metastases were detected in a further nine patients. In 85 patients with full staging criteria at presentation, 28 (33 per cent) were Stage 1, 8 (9 per cent) were Stage 2, 29 (34 per cent) were Stage 3, and 20 (24 per cent) were Stage 4.

Operative treatment

The number of patients who underwent surgery before or after referral to the Royal Marsden was 110, 49 of whom had more than one surgical procedure. Before referral complete excision had been undertaken in 13 patients, all of whom developed local recurrence; partial excision had been undertaken in 31. Following referral, complete excision was performed in 28 patients, partial excision in 62, and biopsy alone in three. No surgery was undertaken in 27 patients, 19 of whom had already undergone surgery elsewhere.

Resectability

Information on the involvement of adjacent viscera at operation was available in 110 patients (*Table 2*). A linear relationship was noted between the number of organs involved and the size of the tumour ($F=8{\cdot}6$; $P=0{\cdot}005$). No correlation was found between the grade of the tumour, its size, or the number of organs involved. Of patients who underwent complete excision of retroperitoneal sarcoma, 70 per cent had received no previous surgical treatment

Completeness of excision was related to the nature of organ involvement (*Table 2*) Analysis by stepwise logistic regression revealed that involvement of a single organ was the principal factor associated with complete excision (*Table 3*). Histopathological subtype had no independent effect on resectability

Operative morbidity and mortality

There were no deaths directly attributable to surgery Six patients developed wound infections, three had major haemorrhage requiring transfusion and/or surgery, one developed a small bowel fistula, one a ureteric fistula, and one a pulmonary embolism.

Non-operative treatment

Before referral 14 patients had received radiotherapy and 11 systemic chemotherapy. Following referral, six patients were treated with radiotherapy alone and 21 were given radiotherapy for residual disease after partial surgical excision. Seven patients were treated with chemotherapy alone. Three patients were given chemotherapy preoperatively and 39 subsequently for residual disease Chemotherapy was given to 17 patients in the perioperative period for metastatic disease

Follow-up

Fifty-five patients died with a median follow-up time of 11 months (range <1–146). Follow-up details exceeding 24 months were only available for one-third of the survivors because most were treated in the latter part of the review period and because patients from other centres were lost to follow-up

Recurrence

Of 28 patients who underwent complete excision of tumour after referral, 13 developed local recurrence The cumulative probability of local recurrence was 31 per cent (95 per cent C I 15–52) at 2 years and 85 per cent (95 per cent C I. 56–99) at 5 years. Metastases were present in two patients before surgery

Table 2 *Organ involvement in 93 patients**

Organ	Cases	Complete excision
Kidney	24	11
Colon	16	4
Small intestine	14	4
Pancreas	14	5
Mesentery	13	3
Ureter	12	4
Spleen	11	5
Iliac vessels	11	1
Inferior vena cava	10	3
Bone	9	4
Aorta	8	1
Stomach	7	2
Omentum	6	2
Abdominal wall	6	2
Superior mesenteric artery	5	1
Liver	3	0
Bladder	4	0
Psoas	1	0
Other	18	6

* 56 patients had more than one organ involved

Table 3 *Regression analysis for resectability*

Step number	Covariate	Improvement in log likelihood
1	Number of organs involved	$\chi^2=4{\cdot}6$ $P=0{\cdot}03$*
2	Involvement of kidney/ureter	$\chi^2=3{\cdot}29$ $P=0{\cdot}07$

* A significant improvement in log likelihood means that the outcome predicted from the model of 'best fit' agrees more closely with the observed outcome than that predicted by the basic regression equation

and five developed them during follow-up. Of the 91 patients who did not have detectable metastases at presentation, 17 developed them during follow up.

Survival

The overall 2- and 5-year survival rates following referral were 53 per cent (95 per cent C.I. 42–63) and 29 per cent (95 per cent C.I. 17–42) respectively. On univariate analysis factors having significant effects on survival were performance status at presentation (*Figure 2*), histological grade (*Figure 3*), completeness of surgical excision (*Figure 4*), and treatment with radiotherapy ($\chi^2=4{\cdot}14$, $P=0{\cdot}04$). The presence of metastases at presentation was associated with a poor prognosis ($\chi^2=3{\cdot}95$, $P=0{\cdot}04$). There was no significant difference in survival according to tumour size ($\chi^2=0{\cdot}98$, n.s.), histopathological subtype ($\chi^2=2{\cdot}29$, n.s.), number of organs involved ($\chi^2=0{\cdot}10$, n.s.), surgery before referral ($\chi^2=0{\cdot}41$, n.s.) or treatment with chemotherapy ($\chi^2=2{\cdot}60$, n.s.). Patients with involvement of the upper urinary tract did not have a significantly better prognosis than those with other organs involved ($\chi^2=1{\cdot}10$, n.s.).

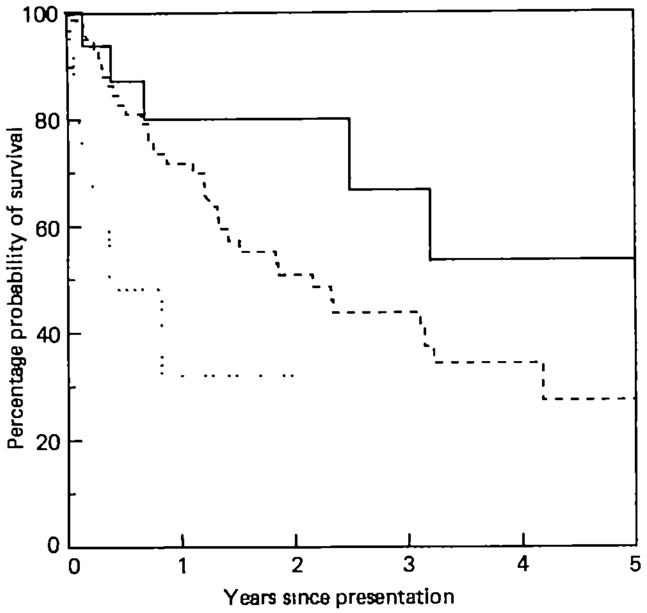

Figure 2 *Survival according to performance status (PS)* ——, *PS=0*, ---, *PS=1*, · · ·, *PS>1*. $\chi^2=7{\cdot}9$ *(trend)*, P=0·005

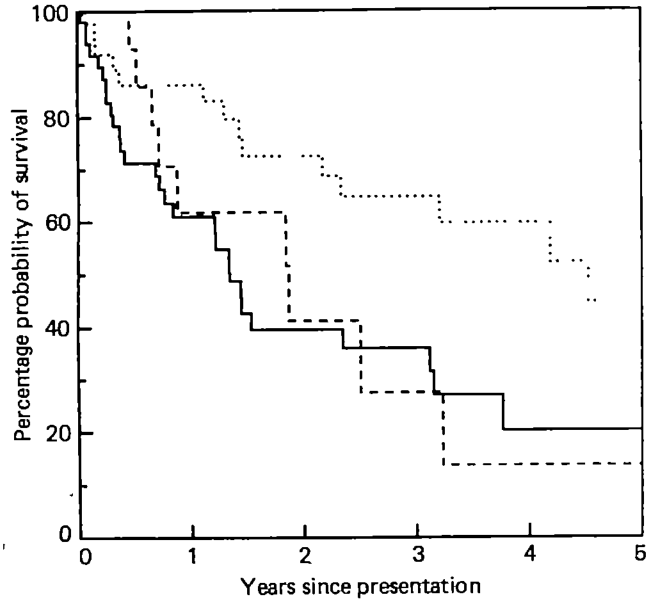

Figure 3 *Survival according to tumour grade.* ——, *High*, ---, *intermediate;* · · · · ·, *low.* $\chi^2=7{\cdot}55$ *(trend)*, P=0·006

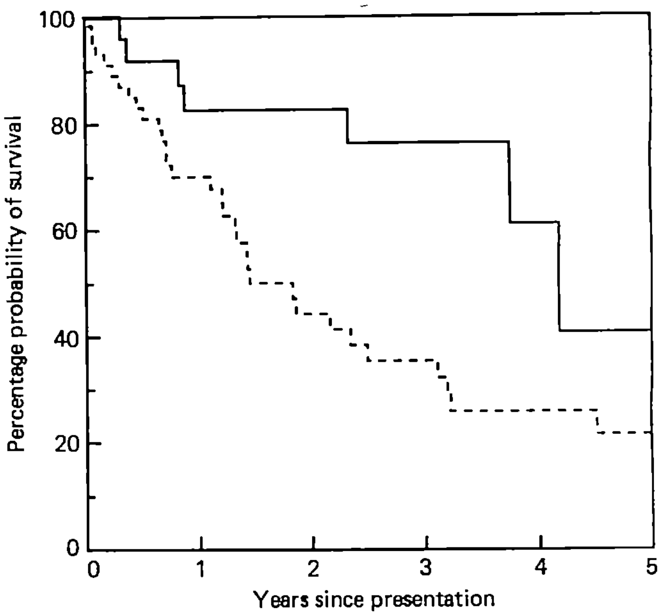

Figure 4 *Survival according to completeness of excision* ——, *Complete excision;* ---, *incomplete excision* $\chi^2=5{\cdot}44$, P=0·02

Table 4 *Multivariate analysis of risk factors for overall survival*

Covariate	Relative risk of death	95 per cent confidence interval
Size		
>5 cm	1	
<5 cm	0·3	0·03–2·2
Metastases		
No metastases	1	
Metastases	2·5	1·2–5·0*
PS=0	1	
PS=1	1·8	0·6–4·8
PS>1	4·7	1·5–15·3*
Excision		
Incomplete	1	
Complete	0·3	0·1–0·8*
Grade of tumour		
High grade	1	
Intermediate grade	0·8	0·4–1·8
Low grade	0·4	0·2–0·8*

* Significant at the 5 per cent level because the 95 per cent confidence intervals for the relative risk of death for the variable do not span unity

On multivariate analysis, principal factors associated with a favourable prognosis were absence of metastases and good performance status (i.e. low score) at presentation, low histological grade, and complete surgical excision (*Table 4*).

There were no significant differences in the distribution of other prognostic variables where a specific prognostic variable was unknown and 'missing values', analysed as a separate covariate, did not have a significant effect on survival.

Discussion

Soft tissue sarcomas account for less than 1 per cent of all malignant tumours[18]; 10 per cent are located in the retroperitoneum[19–23] and, apart from lymphomas, they are the most common mesothelial tumours in this situation[19–29]. The estimated incidence of retroperitoneal sarcoma is 0·2–0·5 per 100 000 population[27,28]. Large series are usually retrospective over periods of time up to 20 years[1,8].

Disadvantages of such retrospective analyses are that accurate data collection is often difficult and treatment policies change. However, the outcome of treatment usually depends on a multitude of biological and therapeutic factors whose individual importance cannot be adequately assessed unless a large number of patients are analysed. In this study, data were not always complete and details of earlier treatment were often imprecise. Missing values were therefore included as a separate variable in the analysis which concentrated on surgical aspects of treatment.

Classification of soft tissue tumours has been refined by the introduction of new immunohistochemical techniques[12]. For example, malignant fibrous histiocytoma (MFH) is now recognized as histologically distinct from fibrosarcoma[30]. Contrary to some reports[1,23,31–33], though consistent with others[8], no evidence of a significant difference in prognosis among the patients with MFH, liposarcoma and leiomyosarcoma (most tumours) was found[1–9,34,35].

According to UICC criteria[14], nearly all patients presented at an advanced clinical stage despite a mean duration of symptoms of only 2 months. More than 90 per cent of tumours exceeded 5 cm in diameter[8], and the clinical stage was principally a reflection of histological grade.

Histological grade has a marked effect on survival; patients with low grade tumours have significantly better survival prospects[5,8]. In this study, the effect was independent of other variables The prognosis of patients with intermediate and high grade tumours was almost identical, suggesting that a two-tier grading system is probably sufficient[8].

Ability to achieve complete excision was related chiefly to the number of organs involved by the tumour, not to its size. The result confirms that even large tumours can be totally excised provided they do not involve multiple organs[3]. There was no evidence that histological subtype influenced resectability as suggested elsewhere[1,6,23]

As in previous studies[1,3,7,8,36,37], adjacent organ involvement was common; like others[1,3,8,28,36–38], a transperitoneal approach was preferred as it provided better access to the main blood vessels related to the tumour In view of the risk of bowel involvement, thorough bowel preparation is advisable as a routine[1]

The actuarial 5-year survival rate was 29 per cent, lower than that reported in some studies[4,8], but survival was measured from the time of presentation to the Royal Marsden Hospital, the most precisely documented date available[17]. As many patients were referred from other institutions the survival rate represents a preselected group of patients which may not be directly comparable to other figures.

Univariate and multivariate analysis demonstrated that survival was significantly better after complete excision of the primary tumour Despite its effect on resectability, multiple organ involvement did not significantly influence prognosis, suggesting that its effect was mediated through its relationship to resectability. After apparently complete excision, however, the cumulative probability of local relapse exceeded 80 per cent at 5 years, a figure consistent with the results of other studies[1,9,23,39]

Our results demonstrate that the prognosis of patients with retroperitoneal sarcoma can be favourably influenced, albeit temporarily, by complete excision of the primary tumour. Those most likely to obtain lasting palliation have low grade tumours. If complete excision is not possible, survival prospects are dismal and radical surgery is probably not worthwhile[6]. Major surgery should probably also be avoided in patients with concurrent metastases, low performance status and a high grade primary tumour unless it is essential for palliation. Distant metastases and multiple organ involvement, which determines resectability, can be established by CT scanning, the investigation of choice for primary and recurrent retroperitoneal sarcoma[1,7,37,38,40]. Tumour grade can be determined by percutaneous CT-guided needle biopsy[27,41,42]. The main prognostic factors on which the decision to attempt resection depend can therefore be determined without necessarily resorting to surgical exploration Future prospects for patients with retroperitoneal sarcoma depend upon the introduction of more effective adjuvant measures than are currently available and are unlikely to be improved by surgery alone.

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Tropic role of enteroglucagon in pancreatic adaptation to subtotal enterectomy

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Proximal small bowel resection causes pancreatic hyperplasia, presumably via a humoral mechanism. Although cholecystokinin can stimulate pancreatic growth, its proximal distribution in the gut makes it an unlikely intermediary after proximal small bowel resection. The potential roles of neurotensin and enteroglucagon were studied, since these hormones are mainly secreted from the ileum and proximal colon. Male Wistar rats ($n = 50$) *weighing 200–250 g were randomized to receive 90 per cent proximal small bowel resection or jejunal transection and resuture (control). Rats were killed at 1 week or 1 month, when plasma was obtained for hormone assay and the pancreas was excised for protein and nucleic acid measurement. Proximal small bowel resection increased circulating enteroglucagon levels by 150 per cent at 1 week* ($P < 0{\cdot}002$) *and by 83 per cent at 1 month* ($P < 0{\cdot}005$)*; neurotensin levels were unchanged. Pancreatic wet weight was 21 per cent greater 1 month after proximal small bowel resection* ($P < 0{\cdot}001$)*. Proximal small bowel resection increased protein, RNA and DNA contents of the pancreas both at 1 week and at 1 month. Since plasma enteroglucagon correlated with these indices of pancreatic mass, enteroglucagon may have a pancreatotropic role (in addition to its enterotropic role).*

Proximal small bowel resection (PSBR) exposes the distal gut both to an increased luminal supply of nutrients and pancreatobiliary secretions, and to an increased blood-borne supply of peptides such as enteroglucagon[1,2]. Adaptive growth of the ileum, which is rapid and sustained, is accompanied by lesser changes in the stomach, duodenum and upper jejunum (as well as the colon)[3–5]. This response in the 'upstream' gut, like that observed in bowel isolated as a Thiry–Vella fistula[3,4], indicates the importance of humoral factors rather than luminal factors. The pancreas shares in the compensatory response to partial enterectomy[6,7] and can adapt to changes in the diet[8,9], again presumably by indirect means.

There are almost as many candidate hormones for the role of 'pancreatotropin' as there are for enterotropic hormones[10–14]. Attention has focused on cholecystokinin (CCK), which can certainly stimulate pancreatic hyperplasia[14], but an extensive PSBR would remove many CCK-secreting cells. Circulating levels of insulin and pancreatic glucagon are unchanged after bowel resection[15]. Although gastrin can produce hyperplasia of acinar and ductal tissue with a corresponding increase in secretory capacity[12], elegant studies in rats with gastrectomy have excluded its involvement in the response to PSBR[7].

Originally isolated from bovine hypothalamus, the tridecapeptide neurotensin is distributed throughout the gastrointestinal tract but especially in the ileum[16]. Chronic administration of exogenous neurotensin induces pancreatic hyperplasia in rats[10,11]. Enteroglucagon, which is secreted mainly from the ileum and proximal colon, has an established role in the adaptive response of the shortened gut[1,17]. The present study was designed to test whether neurotensin and enteroglucagon play a part in pancreatic adaptation to PSBR.

Materials and methods

Animals and operations

Fifty male Wistar rats weighing 200–250 g were housed in groups of five in animal quarters with a 12 h day/night cycle. Standard pelleted rat food (Paterson and the Christopher Hill Group, Porton-diet PRD) and water were available *ad libitum*. After 1 week of acclimatization, animals were randomized to receive either 90 per cent proximal small bowel resection (as measured from the ligament of Treitz) with end-to-end anastomosis ($n = 29$) or jejunal transection and resuture ($n = 21$). Operations were carried out under light ether anaesthesia. A continuous 6/0 silk suture was used for intestinal anastomoses. Food was re-introduced 12 h after the operation. Representatives of resection and transection groups were killed at 1 week and 1 month after the operation without fasting. Plasma was obtained from the portal vein for hormone assay. The pancreas was excised, trimmed free of adherent fat and lymph nodes, and weighed. Small samples were removed for protein and nucleic acid measurement.

Hormone assays

Plasma neurotensin was measured by an established assay using antiserum NT58[18]. Enteroglucagon was measured by a standard radioimmunoassay technique described in full elsewhere[19]. Two assays were carried out, one with an antibody (R50) that fully cross-reacts with glicentin and one with an antibody (RCS5) directed against pancreatic glucagon, which shows no cross-reaction with glicentin. Enteroglucagon levels were derived by subtracting the small proportion of pancreatic glucagon from total glucagon immunoreactivity.

Biochemical studies

Pancreatic tissue was homogenized in phosphate buffered saline (pH 7·5). The concentration of the homogenate was adjusted to 1 mg tissue per ml. Pancreatic contents of DNA and RNA were assayed by the fluorimetric method of Boer[20] but using an excitation wavelength of 536 nm and an emission wavelength of 602 nm. Protein content was determined by the method of Lowry *et al.*[21]. Since body-weight has a profound effect on pancreatic weight[22,23], protein and nucleic acid contents were expressed as mg per 100 g body-weight to correct for this variable, in line with other workers[7,24].

Statistical analysis

Student's *t* test for unpaired data was used for the group analysis, and results are given as mean and standard error of the mean. The Spearman rank correlation coefficient was used to assess correlations between plasma enteroglucagon and nucleic acid contents in rats with PSBR and transection.

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Results

Mortality and weight loss

There were seven early deaths (one from anaesthetic overdose and six from anastomotic leakage), all but one in the resection group. Another three rats with PSBR failed to thrive and were later discarded. Final yields of healthy rats were 10 (1 week) and 10 (1 month) after transection, and 10 (1 week) and 10 (1 month) after resection. Rats with 90 per cent PSBR weighed 6 per cent less than controls at 1 week (210 *versus* 224 g, n.s.) and 15 per cent less at 1 month (270 *versus* 318·5 g, $P<0{\cdot}001$).

Pancreatic weight

Pancreatic growth occurred with age in both groups of rats. In controls, pancreatic wet weight increased from 900 mg at 1 week to 1600 mg at 1 month. In rats with PSBR, pancreatic weight was similar to controls at 1 week (920 mg) but 21 per cent greater at 1 month (1940 mg, $P<0{\cdot}001$).

PSBR increased the pancreatic weight per 100 g body-weight from 405 to 436 mg/100 g at 1 week (n.s.) and from 508 to 722 mg/100 g at 1 month ($P<0{\cdot}001$ (*Figure 1*).

Plasma neurotensin and enteroglucagon (Table 1)

PSBR had no appreciable effect on plasma neurotensin levels either at 1 week or at 1 month. By contrast, PSBR increased circulating enteroglucagon levels by 150 per cent at 1 week ($P<0{\cdot}002$) and by 83 per cent at 1 month ($P<0{\cdot}005$).

Protein and nucleic acid contents (Figure 2)

When pancreatic contents of nucleic acid were expressed per 100 g body-weight, PSBR increased DNA by 45 per cent (1·35 mg *versus* 0·93 mg) at 1 week and RNA by 72 per cent (4·69 mg *versus* 2·73 mg). The RNA:DNA ratio was essentially unchanged (3·47 *versus* 3·04). These increments were sustained at 1 month, DNA being 37 per cent greater (2·31 mg *versus* 1·69 mg) and RNA 41 per cent greater (5·79 mg *versus* 4·10 mg). Once again the RNA:DNA ratio was essentially unchanged (2·60 *versus* 2·47). Likewise, PSBR increased protein content per 100 g body-weight by 5 per cent at 1 week (58·28 mg *versus* 55·74 mg, n.s.) and by 31 per cent at 1 month (96·70 mg *versus* 73·60 mg, $P<0{\cdot}05$).

There was a positive exponential correlation between plasma enteroglucagon and RNA content of the pancreas ($r_S=0{\cdot}862$) and between plasma enteroglucagon and DNA content ($r_S=0{\cdot}642$, *Figure 3*).

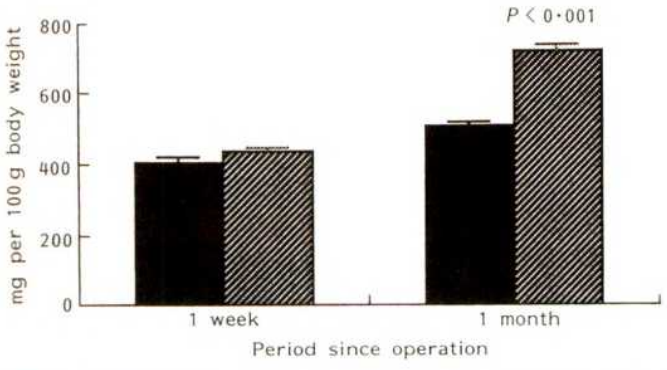

Figure 1 *Mean (s.e.m.) pancreatic weight expressed per 100 g body-weight (BW):* ■, *control;* ▨, *proximal small bowel resection (PSBR)*

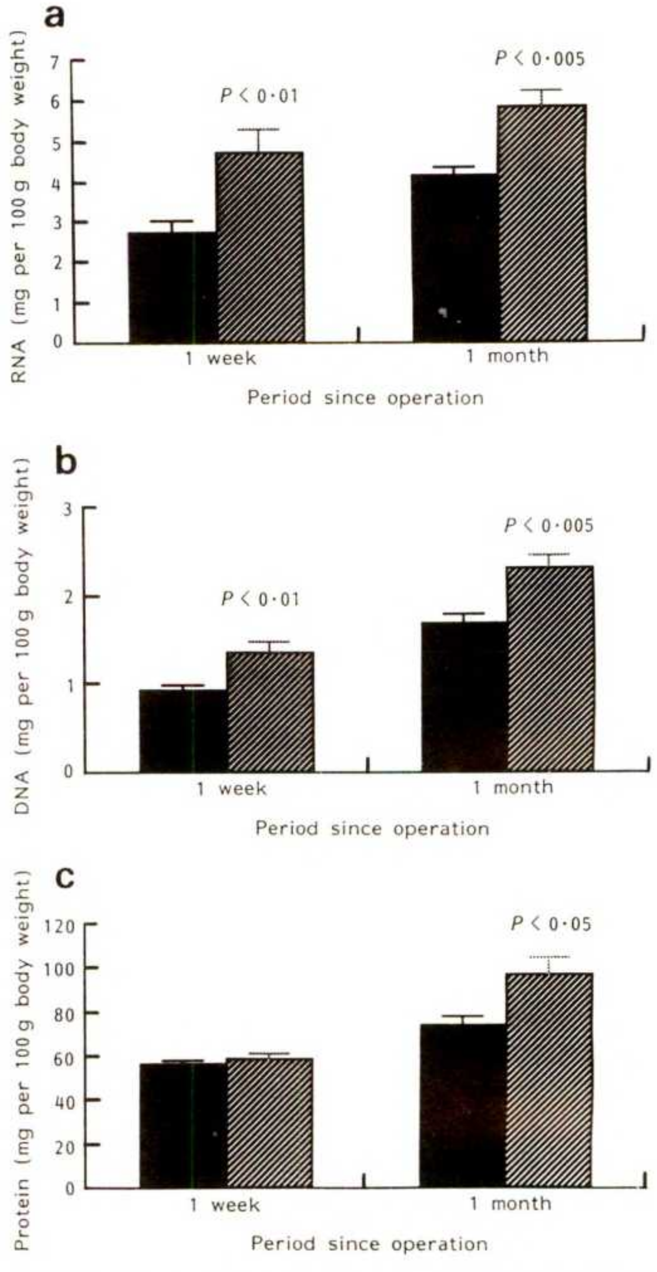

Figure 2 *Mean (s.e.m.) pancreatic contents of* **a** *RNA*, **b** *DNA and* **c** *protein expressed per 100 g body-weight (BW):* ■, *control;* ▨, *proximal small bowel resection (PSBR)*

Table 1 *Mean (s.e.m.) plasma levels of neurotensin (pmol/l) and enteroglucagon (pmol/l) 1 week and 1 month after 90 per cent proximal small bowel resection (PSBR)*

	1 week		1 month	
	Neurotensin	Enteroglucagon	Neurotensin	Enteroglucagon
Control	22·74(7·19)	311·40(30·30)	20·74(4·61)	360·10(41·40)
PSBR	18·92(6·14)	777·00(101·00)**	34·42(9·76)	660·70(75·00)*

* $P<0{\cdot}005$; ** $P<0{\cdot}002$

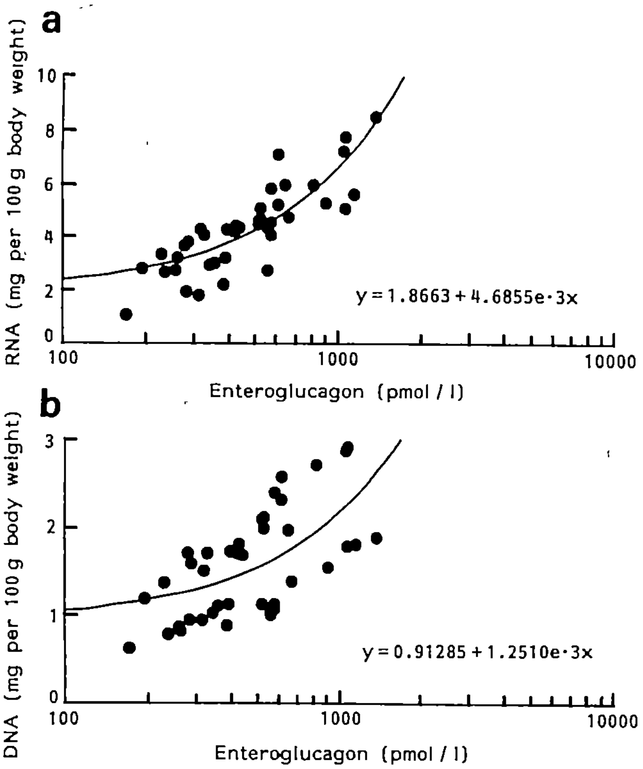

Figure 3 *Correlation between* **a** *plasma enteroglucagon in pmol/l and RNA content in mg/100 g body-weight (BW)* ($r_s = 0{\cdot}862$) *and between* **b** *plasma enteroglucagon in pmol/l and DNA content in mg/100 g body-weight (BW)* ($r_s = 0\ 642$)

Discussion

The increments in pancreatic protein and nucleic acids (with unchanged RNA:DNA ratio) confirm the hyperplastic response of the pancreas to a massive enterectomy. As others have shown[6], hyperplasia becomes less marked with the passage of time. Although increased luminal nutrition explains much of the ileal response to PSBR[17], systemic factors must surely be involved in the pancreatic response to this operation.

Among surgical stimuli to pancreatic growth, small bowel resection seems weaker than pancreatobiliary diversion. We have recently shown that pancreatobiliary diversion actually enhances experimental pancreatic carcinogenesis but 90 per cent PSBR does not[25]. Diversion is known to increase circulating levels of CCK, and the CCK antagonist CR-1409 can inhibit the pancreatic response to diversion[26]. CCK-secreting cells occur in highest numbers in the duodenum and proximal jejunum, but sparsely in the ileum and are virtually absent from the rest of the gut of adult mammals[27]. Since complete removal of the jejunum must lessen the chance that CCK can play a major role in pancreatic adaptation to enterectomy, we have looked for alternative candidates secreted by the distal bowel.

Neurotensin seemed a plausible pancreatotropic factor following PSBR. This operation increases the tissue concentration of neurotensin-like immunoreactivity, an action that is mimicked by intragastric instillation of fat[28]. Moreover, exogenous high-dose neurotensin has a tropic effect on rat pancreas when given subcutaneously for 2 weeks (282 pmol/kg/min, using osmotic minipumps) or intraperitoneally (836 pmol/kg) for 3 days[10,11]. This tropic effect can be demonstrated only when plasma neurotensin level is at least twice the control value. Nevertheless, neurotensin was unchanged in the present study, possibly because of the extent of ileum resected.

There are many glucagon-related compounds released from the intestine: glicentin, oxyntomodulin, glucagon-like peptide I and II and enteroglucagon[29]. All these peptides have an insulinotropic effect on the pancreas, but only enteroglucagon has now been shown to have growth-promoting properties. Hyperphagia may contribute to increased enteroglucagon secretion after small bowel resection, but the compensatory response of the residual intestine is not completely dependent on food intake[3]. Whatever the mechanism, the sustained increase in plasma enteroglucagon after PSBR together with the clearcut correlation between enteroglucagon concentration and nucleic acid contents of the pancreas support the pancreatotropic role of this hormone. A pure preparation of enteroglucagon (or its antagonist) could be used to confirm its influence on the adaptive response of the pancreas and intestine to common operations, such as small bowel resection, but such a preparation is not yet available.

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Clinical and functional results of abdominal rectopexy for complete rectal prolapse

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Between 1977 and 1987, 53 patients underwent polyvinyl alcohol sponge rectopexy for complete rectal prolapse. The mean follow-up period was 36·7 months. Full thickness prolapse recurred in two patients (3·8 per cent). Infection around the prosthesis and faecal impaction developed in two patients each. Continence improved significantly after operation, particularly in those under 70 years of age (P = *0·028,* χ^2 *test) and nulliparous women* (P = *0·026,* χ^2 *test). Bowel function was generally unchanged after rectopexy; in particular only eight patients (15 per cent) had significant postoperative constipation.*

The recurrence rate following abdominal rectopexy is now below 4 per cent[1–5]. There is, however, no consensus on the operation of choice. In the UK, the Wells' rectopexy[6] (or a variant thereof) is most commonly performed, whereas in the USA and Australasia the Ripstein procedure is preferred. As the recurrence rates after these procedures are similar, attention needs to focus on the functional outcome of the operation. Good results have been reported following suture rectopexy combined with sigmoid resection[5], although resection with anastomosis adds considerably to the magnitude of the procedure which is often performed in elderly patients.

At present there are few indicators to suggest which patients will have a poor functional result following operation. We have examined the preoperative history of 53 patients with complete rectal prolapse who underwent Wells' rectopexy in an attempt to identify any variables which predict a poor functional outcome.

Patients and methods

Between 1977 and 1987, 53 patients underwent polyvinyl alcohol sponge abdominal rectopexy for complete rectal prolapse. The average age was 59·9 years (range 14–90) with the expected preponderance of female patients (46 women and seven men).

Preoperative details

Preoperative information was obtained from the case notes. After operation all patients were seen routinely in surgical outpatients. This was supplemented by a questionnaire which enquired specifically about details of continence, bowel habit and patient satisfaction in 46 patients (87 per cent). The information obtained was entered into a computerized database for analysis.

The mean symptom duration was 45·1 months. Thirteen (25 per cent) patients had undergone previous anorectal surgery Thiersch wire insertion (four), haemorrhoidectomy (three), excision mucosal prolapse (two), perianal repair (two), Delorme's procedure (one) and sphincter repair (one). In the female group, 14 patients (30 per cent) had a prior hysterectomy, and pelvic repair had been performed in four (9 per cent) Fifteen women were nulliparous, eight had one child, 12 had two children and 11 had three or more.

Continence was classified after Browning and Parks[7] (*Table 1*). Grades 3 and 4 were considered unacceptable. No distinction was drawn between occasional and regular episodes of incontinence. Only 16 (31 per cent) patients had acceptable faecal control before operation (*Figure 1*); 34 per cent of those under 70 years of age and 24 per cent of those over 70. Forty per cent of nulliparous women were continent, while only 26 per cent of those with children were found to be continent.

In terms of faecal frequency, most had a normal bowel habit (*Figure 2*) Constipation was defined as the passage of three or fewer bowel actions a week or marked straining at stool; faecal frequency was more than three bowel actions a day.

Operative details

All operations were performed by the consultant or by a senior registrar under supervision. Patients routinely received three doses of a cephalosporin intravenously as antibiotic prophylaxis. The steps of the operation were:

1. Rectum mobilized posteriorly to the level of the coccyx
2. Lower part of the lateral ligaments preserved
3. Polyvinyl alcohol sponge sutured posteriorly to presacral fascia Sponge wrapped anteriorly around two-thirds of the rectal circumference and sutured to the muscular layer of the rectum
4. Closure of the anterior peritoneal pouch
5. Uterine ventrofixation performed in 16 of the female patients.

Results

There was no operative mortality, but non-specific complications developed in eight (15 per cent). Four complications directly related to the rectopexy Infection around the implanted sponge, which presented with a discharge of pus *per rectum* developed in two patients; in both an opening was visible in the posterior wall of the rectum on sigmoidoscopy and removal of the prosthesis was possible with rapid resolution of the sepsis[8]. Two others were admitted for management of faecal impaction.

Full thickness rectal prolapse recurred in two patients (one man, one woman) within 18 months of operation. Mucosal prolapse was noted in ten patients (19 per cent). This was generally managed by injection or banding except for three patients who underwent Delorme's procedure (submucosal excision of the redundant mucosa).

Satisfactory continence improved from 30 per cent to 56 per cent (*Figure 1*). Only six patients were incontinent for solid stool after operation. Individual changes are shown in *Figure 3*. It is disappointing to note that control decreased in ten patients, with only four having a minor change; in five of these patients there was recurrent complete or mucosal prolapse. Postanal repair was necessary in two cases.

A higher proportion of nulliparous women are continent after operation (80 per cent compared with 45 per cent, $P = 0{\cdot}026$, χ^2 test). Those who are continent after rectopexy

Table 1 *Classification of continence*

Grade 1	Fully continent for flatus and stool
Grade 2	Continent for stool but not for flatus
Grade 3	Incontinent for liquid stool
Grade 4	Incontinent for solid stool

After Browning and Parks[7]

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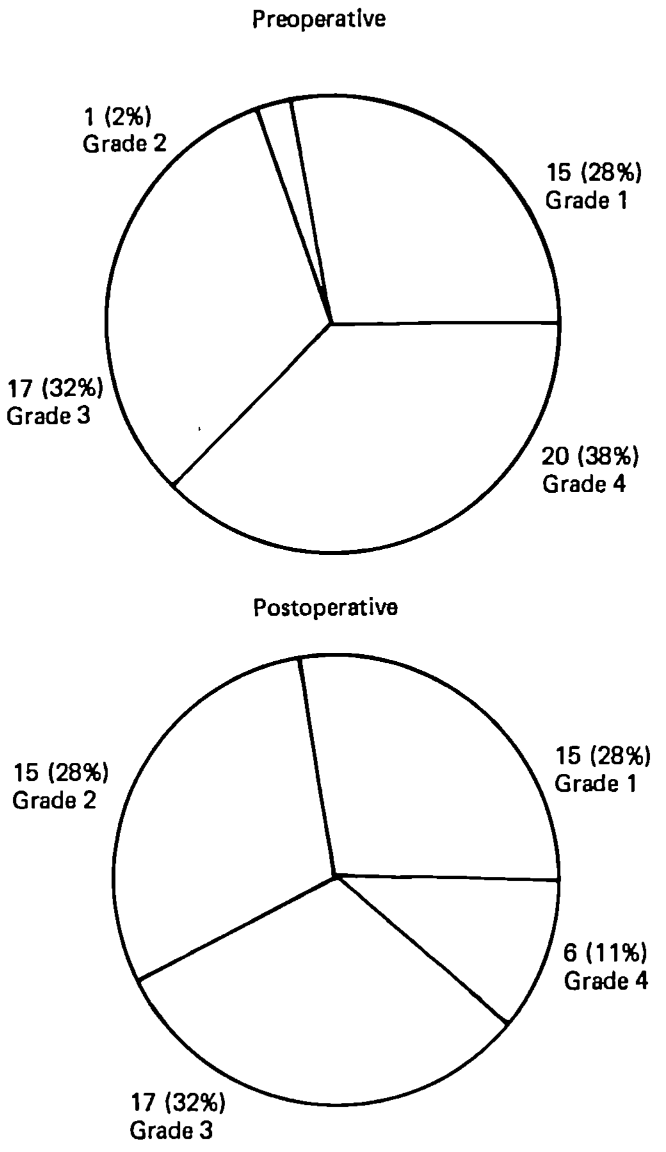

Figure 1 *Preoperative and postoperative continence grading*

tend to be younger than those who remain incontinent (54·7 years compared with 65·7 years) There was no difference in age between the parous and nulliparous patients. Change in continence appeared unrelated to length of symptoms, bowel habit, previous anorectal surgery, hysterectomy or whether ventrofixation was performed.

In the series as a whole there was little change in bowel habit (*Figure 2*), although in some patients the results were unpredictable and unrelated to preoperative assessment. Only eight (15 per cent) patients had postoperative constipation.

When asked, 62 per cent of patients were very satisfied with the procedure, 28 per cent were moderately satisfied and 10 per cent were dissatisfied because of either recurrent prolapse or continuing incontinence.

Discussion

Over the past 20 years, abdominal rectopexy has become the accepted management of complete rectal prolapse. Several series report no mortality following operation[2,4,5,9,10] despite operating on a mostly elderly population. Most of the larger studies record a full thickness recurrence rate of below 4 per cent[1–4,10,11]. The functional results have not been explored in the same detail

All workers have demonstrated an improvement in continence following operation, with between 43 per cent and 64 per cent of those who are incontinent preoperatively regaining control after surgical intervention[1–3,5,10]. However, the figures for postoperative continence vary from 52 per cent to 89 per cent, which is due in part to different definitions of continence. Our results would suggest that patients under 70 years of age and nulliparous women are significantly more likely to be continent after rectopexy. Unlike Bomar[12], we did not find that preoperative duration of symptoms influenced results.

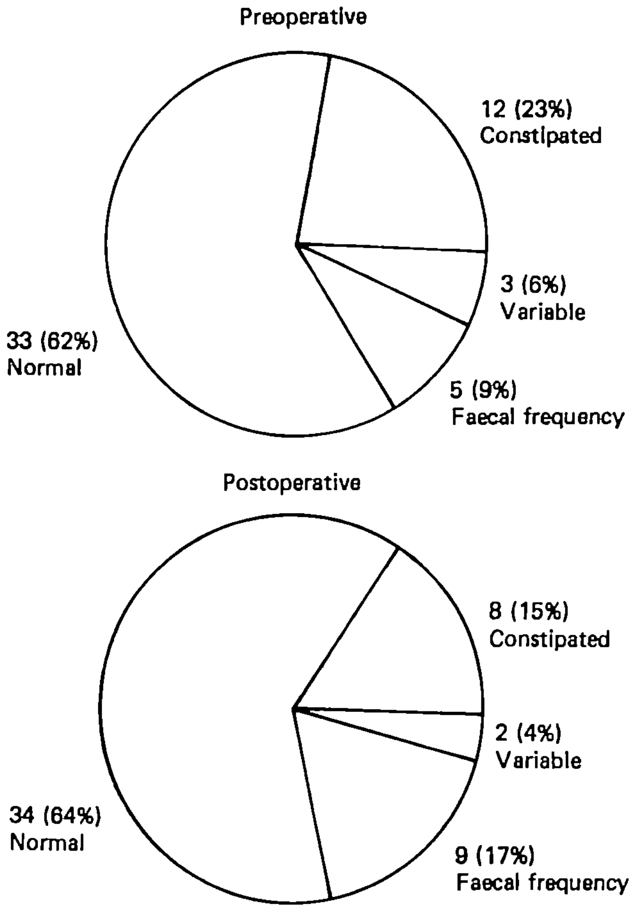

Figure 2 *Preoperative and postoperative bowel habit*

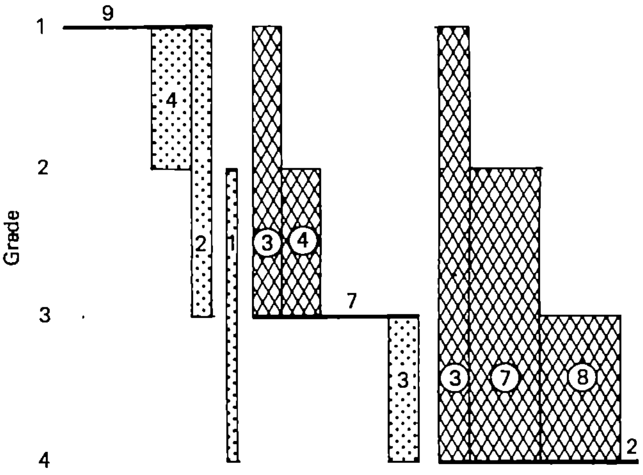

Figure 3 *Changes in continence after operation for individual patients* ▨, *Continence improved,* ☐, *continence deteriorated,* —, *no change Numbers represent number of patients*

Parks showed that patients with faecal incontinence and complete rectal prolapse have abnormal perineal descent on straining, which led to traction injury of the pudendal nerves resulting in denervation of the pelvic floor musculature and sphincter mechanism[13]. This may exacerbate pudendal nerve damage which can occur after childbirth[14], and may possibly explain why continence results are poorer in parous patients.

Ripstein[15] also found that a higher percentage of young patients regained continence. Women over 70 years old have been shown on manometry to have diminished function of both internal and external sphincters[16]; thus the capability for regaining control is decreased in the elderly.

It was disturbing to note that control deteriorated in ten patients. This may in part represent inaccuracy in obtaining preoperative information. None the less, five of the patients had either recurrent mucosal or complete prolapse, and five others had increased faecal frequency which may have 'unmasked' control defects. All patients who deteriorated to Grade 3 or 4 were multiparous women.

Our postoperative constipation rate of 15 per cent is low compared with other series where rates of up to 47 per cent have been recorded[1,9–11,17]. The rate of constipation appears higher with the Ripstein procedure[1,9,11,17] and may be associated with sling placement. A survey of 1111 patients who had undergone the Ripstein procedure revealed that 16·5 per cent had sling-related problems, with 6·7 per cent developing faecal impaction, and 4·1 per cent needing reoperation[18]. Watts *et al.*[5] believe that sigmoid redundancy is responsible for some cases of postoperative constipation and advocate sigmoid resection with suture rectopexy. As we have not found postoperative constipation to be a problem we cannot advocate this larger procedure which exposes patients to anastomotic problems with an associated reoperation rate of 2 per cent. One reason for the low constipation rate may be the preservation of the upper part of the lateral ligaments.

In conclusion, this series has a morbidity and mortality rate similar to other studies. While many patients will have improved continence after rectopexy, prognosis should be guarded in parous patients, particularly if aged over 70 years, as their control may remain unchanged or even deteriorate. These patients may well benefit from subsequent postanal repair. Bowel habit is little affected by the operation and underlying abnormalities may well persist.

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Emergency laparotomy in patients with AIDS

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The presentation, operative management and final diagnosis were reviewed in 28 patients with AIDS (27 men and one woman) who underwent emergency laparotomy. On clinical and radiological examination, six patients showed features of toxic megacolon, five patients had small bowel obstruction, six patients had localized peritonitis and three had perforated viscus with generalized peritonitis. The most common disease processes were acute colitis in seven patients (associated with cytomegalovirus (CMV) infection in six), intra-abdominal lymphoma in five patients, acute appendicitis in five patients (associated with CMV infection in two), and atypical mycobacterial (MAI) infection in four patients. Two perioperative deaths occurred: one in a patient with acute pancreatitis and a second with generalized peritonitis. Later deaths were due to progression of AIDS, and patient survival at 1 month, 3 months and 6 months was 89 per cent, 64 per cent and 48 per cent, respectively. Lower operative mortality than in previously reported series may be due to earlier intervention in CMV toxic megacolon. Surgery, however, conferred less benefit in patients with acute abdominal pain from MAI infection or lymphoma. With careful patient selection, emergency laparotomy may achieve worthwhile palliation in patients with AIDS.

It is estimated that there are over 50 000 HIV antibody-positive individuals in the UK who will eventually develop AIDS[1]. Although some 12 per cent of patients with AIDS experience abdominal pain[2], only 5 per cent of these patients with abdominal pain require surgery[3,4]. This includes a small group who develop acute abdominal symptoms which suggest the need for emergency laparotomy. We have reviewed the experience of emergency laparotomy in three inner London hospitals whose HIV units have treated approximately 2000 patients with AIDS, representing some 70 per cent of all patients with AIDS within the UK[5].

There were three aims to this study: first, to determine the range of conditions which produce acute abdominal symptoms in patients with AIDS; second, to determine whether the development of such symptoms is an agonal phase of AIDS in which emergency laparotomy confers no benefit; and third, if surgery was helpful, to define how those patients who were likely to benefit might be identified before emergency operation.

Patients and methods

The case notes of all patients with AIDS undergoing emergency laparotomy over a 3-year period (September 1987–August 1990) at the Westminster, St. Mary's and the Middlesex Hospitals were reviewed. Only HIV-positive patients whose disease fell within the Centres for Disease Control (CDC) Group 4 classification[6] were included. Patients undergoing elective laparotomy (e.g. for retroperitoneal lymph node biopsy or splenectomy for thrombocytopenia) were excluded.

Details of patient age, sex, risk category, stage of HIV disease, presenting symptoms and signs, radiographic findings, preoperative diagnosis, operative findings, definitive diagnosis and postoperative survival were recorded. Laparotomy was performed in each case by a consultant surgeon or senior registrar, with adherence to the operating theatre guidelines for inoculation-risk patients[7–9]. Follow-up (range 30–790 days) was to the last recorded clinic visit or to the last contact with a member of the HIV nursing or medical service.

Results

Twenty-eight patients with AIDS (19 patients from Westminster, six from St. Mary's and three from the Middlesex Hospital) underwent emergency laparotomy during the 3-year period up to August 1990. There were 27 male patients who were in the higher risk group (26 patients were homosexual and one was bisexual) and one female who had acquired HIV from a blood transfusion. The mean patient age was 36·1 (range 21–52 years).

Source of referral and past medical history

Twenty-two patients were in-patient referrals from physicians with a special interest in AIDS. Three patients were admitted via the Accident and Emergency Department and three by medical teams not primarily involved with HIV patients. In 26 patients a diagnosis of AIDS (CDC Group 4) had been made at the time of referral for surgical opinion. The remaining two patients were known to be HIV antibody-positive (CDC Group 2) and AIDS was diagnosed as a result of emergency laparotomy. Twelve patients were receiving anti-HIV therapy (zidovudine), seven anti-CMV therapy (foscarnet, ganciclovir), four anti-herpes therapy (acyclovir), four prophylaxis against *Pneumocystis carinii* (co-trimoxazole), one chemotherapy for Kaposi's sarcoma (bleomycin) and one chemotherapy for lymphoma (cyclophosphamide and prednisolone).

Presenting symptoms and signs

All patients referred for surgical opinion had severe abdominal pain which was generalized in seven patients. In the remaining 21 patients in whom the pain was localized, the site of maximal tenderness was the central abdomen in eight patients, the right iliac fossa in five patients, the left upper quadrant in two patients, the lower abdomen in two patients, the right side of the abdomen in one patient, and was not specified in three patients. The median duration of pain was 4·2 days, but ranged from a few hours to 90 days. Eleven patients also complained of either diarrhoea or bloody diarrhoea.

Four patients had physical signs consistent with generalized peritonitis, five had localized peritonism, and the remaining 19 patients had abdominal tenderness without rigidity. Chest or plain abdominal radiographs showed features of small bowel obstruction in five patients, colonic dilatation in five patients,

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Table 1 *Preoperative diagnosis, postoperative diagnosis, and surgical procedures undertaken in 28 patients undergoing emergency laparotomy*

Diagnosis					
Before operation	No. of patients	After operation	No of patients	Operative procedure	No of patients
Toxic megacolon	6	CMV colitis	2	Colectomy and ileostomy	4
		CMV and Crohn's colitis	1		
		CMV and ulcerative colitis	1		
		CMV and Kaposi's sarcoma	1	Right hemicolectomy	1
		Haemorrhagic pancreatitis	1	Lavage and drainage	1
Small bowel obstruction	5	Ileal lymphoma	2	Small bowel resection	2
		Adhesions	1	Division of adhesions	1
		Secondary adenocarcinoma	1	Bypass and biopsy	1
		Small bowel volvulus	1	Small bowel resection	1
Perforated viscus	3	Perforated CMV colitis	1	Colectomy and ileostomy	2
		Salmonella and Crohn's colitis	1		
		Perforated ileal lymphoma	1	Small bowel resection	1
Appendicitis	6	Appendicitis	5	Appendicectomy	5
		Negative laparotomy	1	Laparotomy only	1
Uncertain	8	MAI infection	4		
		Para-aortic node enlargement	1	Node biopsy	1
		Liver, spleen and node enlargement	2	Node and liver biopsy	2
		Massive splenomegaly	1	Splenectomy and liver biopsy	1
		Disseminated B cell lymphoma	1	Gastrojejunostomy and biopsy	1
		Right-sided colonic lymphoma	1	Right hemicolectomy	1
		Spontaneous splenic rupture	1	Splenectomy	1
		Primary peritonitis	1	Peritoneal lavage	1

CMV, Cytomegalovirus; MAI, *Mycobacterium avium-intracellulare*

and free air under the diaphragm in three patients. *Table 1* shows the preoperative diagnoses that were made on the basis of these findings.

Laparotomy

The median interval from surgical referral to laparotomy was 1·4 days (range a few hours to 21 days). The laparotomy findings and operative procedures carried out are detailed in *Table 1*. In 75 per cent (21 of 28) of cases, the operative diagnosis fell into one of four categories: acute colitis, intra-abdominal lymphoma, appendicitis or *Mycobacterium avium-intracellulare* (MAI) infection.

Of the seven patients with acute colitis and toxic megacolon or perforation, CMV was identified in six patients and in one patient *Salmonella* was isolated from preoperative stool samples. Three patients had histological features of inflammatory bowel disease, suggestive of ulcerative colitis in one patient and Crohn's disease in two patients Total colectomy with ileostomy was performed in six patients; the rectal stump was either closed (four patients) or brought out as a mucous fistula. Right hemicolectomy was performed in a seventh patient with more limited CMV colitis associated with ileocaecal intussusception of a Kaposi's sarcoma.

Intra-abdominal lymphoma was found in five patients, involving the ileum in three patients, the ascending colon in one patient, and the small bowel and peritoneum in one. The diagnosis of lymphoma was known preoperatively in only one patient (who perforated an area of small bowel lymphoma following chemotherapy) and was suspected from CT scan appearances in a second patient. In all patients, histology confirmed lymphoma of the non-Hodgkin's type (B cell lymphoma).

The diagnosis of MAI was not made before operation, although it was suspected in two of the four patients subsequently found to have MAI, because of fever and marrow suppression. These patients were systemically very ill, despite having less marked abdominal signs than, for example, patients with acute CMV colitis. The patient with MAI who underwent splenectomy had the clinical features of refractory septicaemic shock, but responded rapidly following removal of a massively enlarged spleen. MAI was subsquently isolated from this patient's bone marrow.

The clinical presentation of acute appendicitis in AIDS patients was similar to that in the non-HIV infected population. Laparotomy findings confirmed appendicitis in five patients, and histological features suggesting CMV infection in the appendix were present in two of these patients

Heavy cryptosporidial infestation was noted in necrotic small bowel from the patient with small bowel volvulus (*Table 1*). *Cryptosporidia* are commonly isolated in the gut flora of patients with AIDS[10] and their presence here was not thought to have contributed to the volvulus. No primary site for the case of disseminated adenocarcinoma was identified, and no cause for the spontaneous splenic rupture could be established.

Perioperative mortality

Three patients died during the first 30 days after emergency laparotomy, a perioperative mortality rate of 11 per cent. One patient with generalized purulent peritonitis, for which no underlying cause was found, died on the first postoperative day. One patient suspected of having toxic megacolon with radiological colonic dilatation and a serum amylase of 250 IU/l was found at laparotomy to have acute haemorrhagic pancreatitis (serum amylase 1700 IU/l; the following day) and died in the ITU on the fourth postoperative day. The pancreatitis was unrelated to either biliary calculi or pentamidine therapy[11]. A third patient with advanced intra-abdominal lymphoma died on the 20th postoperative day.

Postoperative outcome

Median in-patient stay following surgery was 28·9 days (range 8–122 days). The survival rate was 64 per cent (16 of 25 of evaluable patients alive) at 3 months after emergency laparotomy. Three of the five patients with abdominal lymphoma, and two of the four patients with MAI infection, died within this period.

The survival rate was 48 per cent (10 of 21 of evaluable patients alive) at 6 months after surgery Two patients who had undergone colectomy and ileostomy formation for acute colitis were well enough to undergo elective ileorectal anastomosis during this period.

Discussion

This study describes the largest experience so far reported of emergency laparotomy for the acute abdomen in patients with AIDS. Previous reports of emergency surgery in patients with AIDS have recorded a higher operative morbidity[12,13] and mortality[14,15]. Wilson *et al.*[14] reported a 1 month mortality rate of 46 per cent in 14 patients who underwent emergency laparotomy. The wide discrepancy between these results and our mortality rate of 11 per cent may in part be explained by earlier surgical intervention in our patients. Although our patients were by definition immunodeficient, it does appear that they were able to withstand bowel resection after major peritoneal inflammation and contamination. This suggests that some patients with AIDS who develop acute abdominal symptoms may be helped by emergency surgical intervention.

These patients represent a very small (1–2 per cent) proportion of the AIDS population treated at these hospitals, and critical patient selection is essential. An important factor in achieving a low perioperative mortality rate is close liaison between physicians and surgeons with an expertise in AIDS to make an accurate preoperative diagnosis and avoid unnecessary surgery. In our series, two patients underwent inappropriate laparotomy, a patient in whom toxic megacolon was suspected and the diagnosis of pancreatitis not made preoperatively, and a patient with advanced AIDS where appendicitis was suspected but laparotomy findings proved normal. In addition, three of the four patients with acute abdominal pain and MAI infection underwent only node or liver biopsy at emergency laparotomy. Previous isolation of MAI by needle biopsy of either liver or enlarged lymph nodes, or by bone marrow aspiration, might have avoided laparotomy in these patients

Laparotomy should also be avoided in patients with AIDS who have intra-abdominal lymphoma which follows an aggressive course that is unlikely to be influenced by surgery. Although bowel obstruction or perforation was corrected in all the cases with lymphoma in the present study, three of the five patients with intra-abdominal lymphoma undergoing emergency laparotomy died of their disease within 3 months of operation. Steinberg *et al.*[16] noted a similarly poor prognosis in all three of their lymphoma patients who died within 6 months of apparently complete removal of localized tumour. Where MAI infection or intra-abdominal lymphoma is suspected, we therefore suggest attempting to establish a diagnosis by abdominal CT or ultrasound scan with guided needle biopsy[17] to avoid laparotomy.

Wexner *et al.*[15] reported a 71 per cent perioperative mortality rate in eleven patients undergoing emergency surgery for CMV colitis. In our experience, colectomy for toxic megacolon, even after perforation, restored the patient to a period of relatively good health with improvement in weight, haemoglobin and CD4 level. Five of our seven patients undergoing emergency surgery for acute colitis remained alive at 6 months.

Two patients developed acute CMV colitis while receiving anti-viral therapy for CMV retinitis. There were also four other patients undergoing treatment for CMV retinitis who underwent emergency laparotomy in the present study and who did not have acute colitis (lymphoma in two patients, MAI infection in one patient and acute pancreatitis in one patient). Thus CMV retinitis was not predictive of CMV colitis as a cause for the acute abdomen. A history of diarrhoea was also not predictive of acute colitis. Although diarrhoea was present in a majority of patients with colitis, it occurred in patients with MAI infection and lymphoma. Diarrhoea in patients with AIDS is found both in association with opportunitistic organisms[10] and in the absence of any detected pathogens Barone *et al.*[2] noted that diarrhoea from opportunistic infection was present in 12 of 29 AIDS patients with abdominal pain.

Although many patients with AIDS experience abdominal pain, the indications for emergency laparotomy remain similar to those in the population without HIV. The physical signs of an acute abdomen or appearances on plain radiograph suggestive of intra-abdominal free air, or of bowel obstruction or dilatation, should raise the question of emergency laparotomy in a patient with AIDS. The physical signs of acute appendicitis in HIV-positive patients are similar to those in patients without HIV.

Gastrointestinal Kaposi's sarcoma with intussusception of a lesion in one patient who also had CMV colitis proved to be an unusual cause for emergency surgery. Although purple patches of Kaposi's sarcoma are reported as visible on upper and lower gastrointestinal tract endoscopy in one-third of patients with AIDS[10,18], complications from this are rare.

The majority of patients with AIDS who have abdominal pain will not benefit from surgery, and every attempt should be made to avoid laparotomy in patients with AIDS who have abdominal lymphoma or MAI infection. However, emergency laparotomy for the acute abdomen in patients with AIDS, in particular for acute colitis and appendicitis, can offer worthwhile palliation.

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Healing of abdominal incisional hernia in infant rats

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Incisional hernia following major laparotomy in adult humans occurs in 5 per cent of cases. Spontaneous healing of such hernias does not occur. We have devised a model for producing abdominal wall incisional hernia in the rat by dividing the linea alba subcutaneously through a small transverse skin incision. In adult rats (n = *17), an incisional hernia formed and progressively increased in size over 32 weeks. In 3-week-old infant rats* (n = *17), all developed herniation immediately. In eight rats, these hernias progressively increased. In three, the hernias were healed at the third week, but recurred at the fourth, eighth and 12th weeks, respectively. In the remaining six animals, the hernias healed spontaneously at 3 weeks and remained healed. A similar observation of spontaneous healing of incisional hernias in children has been reported in one clinical paper. This animal model provides a useful means of studying the clinical difference between adult and infant with respect to incisional hernia.*

Incisional hernia of the anterior abdominal wall after operation is a well recognized complication of abdominal surgery. Left untreated, these hernias usually progressively increase in size. The incidence of hernia formation following major laparotomy is about 5–7 per cent in adults[1,2]. Little has been written about the incidence, course and outcome of incisional hernia in infants and children. Kiely and Spitz[3] found four examples of incisional hernia following 507 laparotomies in patients under 16 years of age. All four incisional hernias healed spontaneously within 4 months and did not require further surgical intervention. This spontaneous closure of incisional hernia in children is in complete contrast to the experience in adults. An animal model to study the natural history of this condition in adult and infant rats has been devised.

Materials and methods

Animals

Wistar infant and adult rats were used. The infant rats were 3 weeks old and weighed between 60 and 75 g. The adult rats were 12–16 weeks old and weighed between 300 and 470 g.

Operation

A transverse incision of 0·5 cm was made in the skin over the lower part of the abdomen under general anaesthesia (intraperitoneal methohexitone sodium). A plane was developed between the skin and the abdominal wall muscles by blunt dissection cranial to the skin incision. The linea alba and peritoneum were then divided subcutaneously in the midline under normal intact skin (*Figure 1*) The length of this incision was 1·5 cm in infants and 3 cm for adults. The defect was left unsutured The skin incision was closed with a single everting suture of 3/0 silk.

Results

Incisional hernias were consistently produced in both infant and adult rats by the above method. The hernias were all apparent within 24 h of the operation. The maximum diameter of the hernia orifice in the abdominal wall was measured serially at intervals over the next 32 weeks by manual reduction of the hernia before each measurement.

Of the 18 adult rats, one died during the anaesthetic. The rest all developed incisional hernias which increased in size with time (*Table 1, Figure 2*). In the infants, 17 of 18 rats survived the operation and all developed incisional hernias. Subsequently, the fate of these hernias followed three different courses (*Table 2, Figure 2*). Group A consisted of eight infant rats (47 per cent) in which the hernia never healed and, indeed, increased in size with time. Group B consisted of six infant rats (35 per cent) in which the hernia spontaneously healed over a period of 3 to 4 weeks and remained healed at 32 weeks. Group C consisted of three infant rats (18 per cent) in which the hernias spontaneously healed initially but subsequently reappeared at 4, 8 and 12 weeks, and then enlarged with time.

Histological sections of the healed hernia site demonstrated fibrous scar tissue bridging the defect in the muscle wall.

Discussion

Abdominal incisional hernia is rarely reported as a complication of abdominal surgery in human infants even though it is well recognized in adults. This may be due to differences in the ability to heal and regenerate tissues between infants and adults. The observation in adult rats in which these

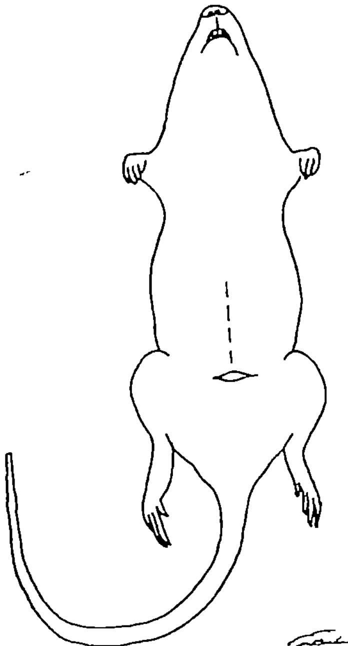

Figure 1 *Operative technique showing transverse skin incision. Dotted line shows muscle incision*

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Table 1 *Diameter of hernia (mm) over a period of 32 weeks in adult rats*

	Weeks								
Animal	1	2	3	4	5	8	12	20	32
1	20	20	20	25	30	30	30	40	40
2	25	25	30	35	40	35	45	55	55
3	25	25	35	40	40	40	40	50	50
4	25	25	30	40	40	35	35	50	50
5	10	10	15	15	15	10	15	20	20
6	30	25	35	45	45	45	45	45	55
7	25	30	35	45	40	40	40	45	50
8	30	30	25	35	30	35	35	35	Died
9	30	30	40	40	40	45	45	50	50
10	35	25		10	15	40	35	45	45
11	30	25	25	25	30	30	30	45	45
12	40	30	40	45	50	50	55	55	55
13	30	30	45	45	40	45	45	55	55
14	30	35	35	45	50		50	50	60
15	35	45	55	50	45		45	40	55
16	30	30	30	30	30		35	35	40
17	25	35	35	35	45		40	45	55

Table 2 *Diameter of hernia (mm) over a period of 32 weeks in infant rats*

	Weeks								
Animal	1	2	3	4	5	8	12	20	32
1	20	20	25	30	25	45	35	40	45
2	20	20	20	25	20	35	40	45	55
3	30	20	20	15	20	30	35	40	40
4	30	25	25	25	20	25	40	45	60
5	40	35	30	35	30	45	45	50	65
6	25	20	20	15	25	25	30	35	40
7	35	25	15	15	30	30	40	35	50
8	30	10	20	20	10	25	35	35	40
9	25	15	–	–	–	–	–	–	–
10	20	5	5	–	–	–	–	–	–
11	10	5	–	–	–	–	–	–	–
12	20	5	–	–	–	–	–	–	–
13	20	10	–	–	–	–	–	–	–
14	20	5	–	–	–	–	–	–	Died
15	10	5	–	–	–	–	15	35	35
16	30	10	–	–	–	15	20	15	20
17	30	15	–	10	10	20	30	35	40

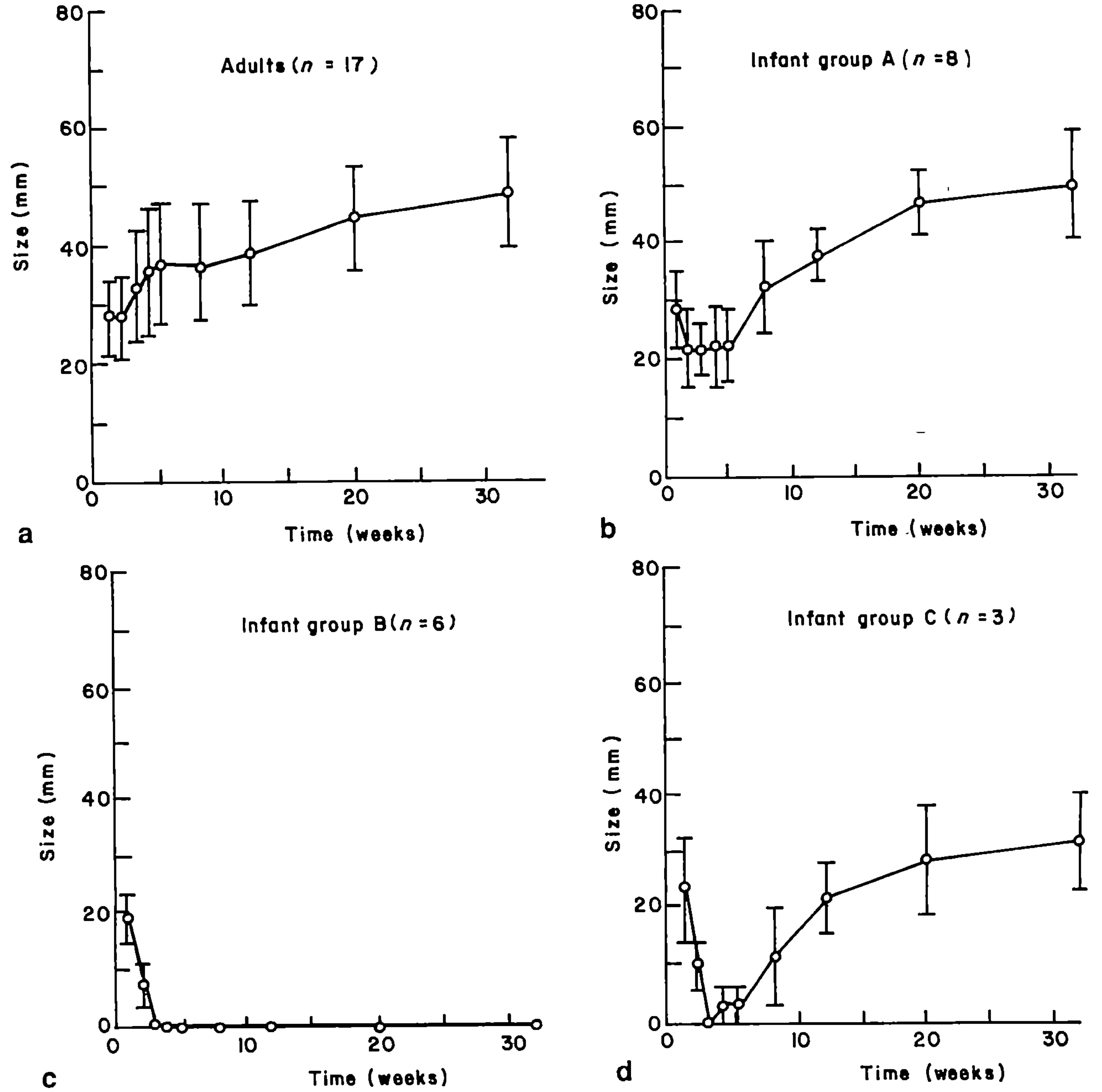

Figure 2 *Graphs showing diameter of hernia orifice in adult and infant rats over a period of 32 weeks* **a** *Adults;* **b** *group A,* **c** *group B, and* **d** *group C (vertical bars represent standard deviation)*

hernias progressively increased in size is no surprise and closely mimicks the clinical situation. However, this experiment clearly demonstrates that incisional hernias in infant rats behave very differently. Nine of 17 infant rats (53 per cent) showed an ability to heal an incisional hernia spontaneously. Histological examination showed that this healing was due to fibrous scarring of the defect in the linea alba.

The factors which determine spontaneous healing in some infant rats and not in others are unknown. There was no sign of infection in the skin wound in any of the animals. Further studies of fibroblast activity and collagen in the wounds of infants and adults are necessary. It would also be interesting to study the difference in composition and arrangement of collagen fibres in normal linea alba and scar tissue; this is being carried out using transmission and scanning electron microscopy in this department.

The technique of inducing a hernia under intact skin was developed to minimize the effect of an overlying skin wound and suture material on the development and progression of the hernia. It also eliminates the problem of wound dehiscence which occurred in earlier experiments in which the skin incision was placed directly over the defect in the linea alba.

The development of secondary hernias in group C at a later stage is probably due to stretching of the scar tissue in the healed wound. This is not dissimilar to the late occurrence of a hernia in a previously healed incision in humans. Such 'late hernia' formation in humans is well recognized and has previously been described[4].

In summary, this experiment demonstrates spontaneous healing of abdominal incisional hernias in infant rats. It would seem to support the observation by Kiely and Spitz[3] of similar healing in human infants. Long-term follow-up of human infants with incisional hernias will be necessary before conclusions can be reached about the extent to which this condition resolves spontaneously, and so about the wisdom of treating the problem conservatively.

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Histopathological evaluation of oesophageal carcinoma: the significance of venous invasion

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Follow-up data on 115 patients who had undergone surgical resection for oesophageal carcinoma were analysed. Histological sections were reviewed for tumour classification, grading and staging, and special stains were used to detect venous invasion. The effect of various factors on survival was statistically analysed using Cox's proportional hazards regression model. In this multivariate analysis lymph node metastasis was the most important variable in the assessment of survival (improvement $\chi^2=7{\cdot}43$, P = 0·006). Venous invasion, which was demonstrated with a frequency of 76·5 per cent (mostly intramural) was the second most important prognostic factor (improvement $\chi^2=2{\cdot}86$, P = 0·09). The relative risk for the presence of both variables was rather modest (3·09).

Oesophageal carcinoma has a poor prognosis, with a 5-year survival rate of only 5 per cent[1]. Numerous studies have examined the predictive value of epidemiological and morphological factors[2]. One objective of histopathological evaluation of malignant neoplasms is predicting biological behaviour. The frequent presence of venous invasion during histological examination of oesophageal cancer prompted a re-examination of histopathological criteria.

Materials and methods

Data from 115 patients with an oesophageal carcinoma who had undergone surgical resection at the University Hospital of Düsseldorf (Germany) between 1978 and 1986 were examined. This included age, sex, time of operation, postoperative survival in months (up to 1 January 1988), location of the tumour, clinically detected distant metastases and autopsy results (performed on 22 patients). Adenocarcinoma at the gastro-oesophageal junction was classified as oesophageal cancer when more than three-quarters of the tumour mass was located in the tubular part of the oesophagus[3]. Patients who died within the perioperative period were not excluded.

Sections of 5-μm thickness from the formalin-fixed and paraffin-embedded tissue from each tumour were studied for WHO tumour classification (typing) and tumour grading using routine haematoxylin and eosin stain and an Alcian Blue-PAS stain (to differentiate between adenocarcinoma and carcinoma with a pseudoglandular component). The histological sections, clinical data and autopsy results (when the patient died within a few months after the operation) were used for TNM-tumour staging. A section from the centre of each tumour was studied for the presence of venous invasion using Weigert's elastic stain and van Gieson stains. Identification of the veins and venules, and distinction from lymphatics, was performed by delineating the elastic fibres in the adventitia and muscle fibres in the media of the vessel wall[4,5] (*Figure 1*). Venous invasion was quantified by a method described in a study on colorectal carcinoma[6]; spread into submucosal or intramuscular venules or veins was classed as intramural venous spread, whereas invasion of venules or veins in the mediastinal fat was categorized as extramural. A venule was defined as a vessel <200 μm in diameter with the absence of a circular muscle coat[7]. The sections were studied independently by two investigators and at different times to avoid interobserver and intraobserver variability and bias.

The statistical evaluation was performed on a personal computer using the BMDP package (BMDP Statistical Software, Inc., Los Angeles, USA). A multivariate analysis was appropriate for evaluating the independent effect of each variable on the response variable. As survival times were of special interest, linear regression was inappropriate for statistical evaluation because the distribution of survival times is generally not normal and because survival analyses often include censored observations[8]. The proportional hazards model of Cox[9] was used. It was carried out with eight covariables (*Table 1*) with a stepwise selection procedure using the maximum partial likelihood ratio method. Covariables were entered or removed on the basis of significance probabilities calculated from a large sample partial likelihood ratio test. The default limit for significance to enter a term by stepwise selection was 0·10, and the limit to remove a term was 0·15. The significance was evaluated with the χ^2 test. The improvement χ^2 measures the change in the log likelihood ratio from the previous step in the model.

TNM stage and tumour invasion of extramural veins were excluded as covariables as these factors were strongly correlated with other variables in the model. Tumour location was excluded in the model as

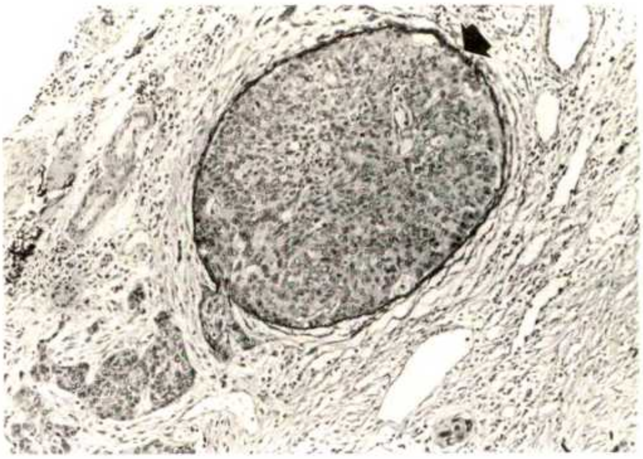

Figure 1 *Histological section showing tumour cells present within a venule. The elastic fibres are clearly visible in the adventitia of the venule (arrow) and not in the wall of the lymphatic vessels. Weiberts elastic stain. Original magnification × 125*

Table 1 *Statistics to enter or remove variables*

Variable	Approximate χ^2 enter	*P*
Sex	1·19	0·2759
Age	0·67	0·4137
Tumour type	0·10	0·7572
Grading	0·35	0·5559
Local tumour extension	3·37	0·0664
Lymph node metastasis	7·43	0·0064
Distant metastasis	2·36	0·1245
Venous invasion	4·71	0·0300

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Table 2 *Summary of stepwise results*

Step	Variable entered	Improvement χ^2	Improvement P	Global χ^2	Global P	Coefficient	Exp(coefficient)	Standard error
1	Lymph node metastasis	7 431	0 006	7·028	0·008	0·6151	1·8499	0 2713
2	Venous invasion	2·864	0·091	9 500	0 009	0 5150	1·6736	0 3207

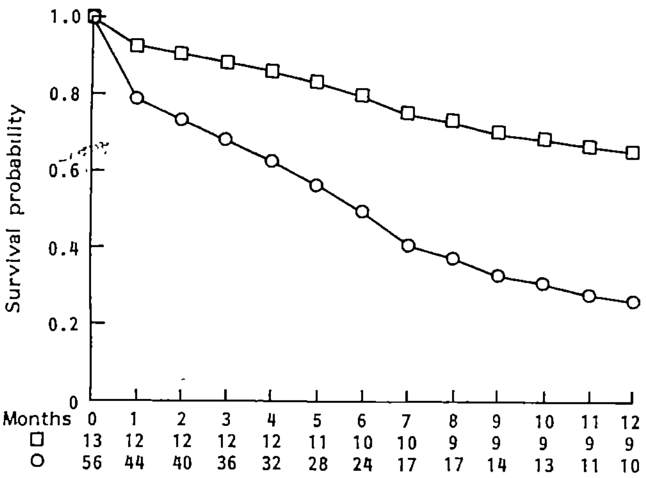

Figure 2 *Estimated survival functions. $S_0(t, N_0, V_0)$ delineates the baseline survival function of cases with no lymph node metastasis or venous invasion. $S(t; N_1, V_1)$ is the survival plot of cases with both lymph node metastasis and venous invasion The number of surviving patients are indicated beneath the graph.* □, $S_0(t, N_0, V_0)$. ○, $S(t; N_1, V_1)$

the number of missing values was too high. With respect to tumour grade, highly or moderately differentiated tumours were combined on the one hand and poorly or undifferentiated tumours on the other.

Results

Of the patients in this study, 83·5 per cent were men and the mean age was 57·9 years. Distribution of tumour location ($n=91$) in the upper, middle and lower part of the oesophagus was 18·7 per cent, 45·1 per cent and 27·5 per cent respectively (the remainder were located between these regions). WHO classification showed that 80·9 per cent were squamous carcinomas, 15·7 per cent adenocarcinomas, 1·7 per cent adenosquamous carcinomas and 1·7 per cent undifferentiated carcinomas. In the lower part of the oesophagus, 44 per cent of the tumours were adenocarcinomas. Almost all tumours were moderately (63·5 per cent) or poorly differentiated (31·3 per cent). Local extension of the tumour was confined to the lamina propria or submucosa (pT_1) in only 7·8 per cent, to the muscularis propria (pT_2) in 20·9 per cent, and in 71 3 per cent there was infiltration of the mediastinal fat tissue (pT_3). Lymph node metastasis (histologically confirmed) was found in 64·3 per cent. Distant metastasis occurred in only 13 per cent of all patients, but was found in 41 per cent of the patients on whom an autopsy was performed. The 1-year postoperative survival rate was 36·5 per cent and the 1-month postoperative mortality rate was 18·3 per cent. Most of the patients (64 per cent) on whom an autopsy was performed had died of bronchopneumonia.

Venous invasion was found in 76·5 per cent of all oesophageal carcinomas; invasion of intramural venules and veins occurred in 67·8 per cent, while invasion of extramural venules and veins was found in 36·5 per cent. Invasion of extramural veins was found in 11·3 per cent.

The results of Cox's proportional hazards regression analysis are shown in *Tables 1* and *2*. Only two variables could enter the final model· lymph node metastasis and venous invasion. The results of the analysis can be described in terms of relative risk by exponentiating the regression coefficient. The death rate for patients with oesophageal carcinoma with lymph node metastasis is $\exp(0{\cdot}6151)=1{\cdot}85$, as large as that for patients with carcinoma without lymph node metastasis. The relative risk for venous invasion is $\exp(0\ 5150)=1{\cdot}61$. The relative risk for both lymph node metastasis (N) and venous invasion (V) is $\exp(0{\cdot}6151+0{\cdot}5150)=3{\cdot}09$. The survival function, S, can be described as follows:

$$S(t;N,V)=\{S_0(t)\}^r \text{ in which } r=\exp(0{\cdot}6151{*}N+0{\cdot}5150{*}V),$$

where $S_0(t)$ is the baseline survival function ($N=0$ and $V=0$ and t is the survival time). Survival curves are shown in *Figure 2*.

Discussion

The significance of venous invasion for survival in patients with colorectal carcinoma has been studied[5,6,10]. Talbot *et al.*[6] showed that venous invasion worsens the prognosis irrespective of Dukes' classification: the corrected 5-year survival rate for patients with Dukes' C without venous invasion was 46 per cent while for those with invasion of thick-walled extramural veins it was only 8 per cent. In a Cox's regression analysis of clinicopathological factors in colon carcinoma, the presence of venous invasion had a significant effect on survival time[11]. A multivariate statistical study of gastric cancer showed that patients with signs of venous invasion had a much poorer outcome irrespective of other epidemiological and morphological factors[12].

There are few previous studies of the prognostic value of blood vessel invasion in oesophageal carcinoma[13,14]. Contrary to our finding of a high incidence of venous invasion, other studies showed blood vessel invasion in 9–20 per cent[13] and in 37 per cent[14]. Only 'large' veins were included in the other studies, whereas venules and veins were included in the present analysis. Tumour cells within vascular channels do not necessarily result in metastatic spread, but simple regression showed a correlation between distant metastasis and venous invasion in extramural veins. A previous study on patients with oesophageal carcinoma showed a high incidence of haematogenous recurrence in tumours with blood vessel invasion[13].

Many earlier studies showed that tumour stage was important but that age, sex, site of the tumour, histological tumour type and tumour grade did not influence survival[15–17]. In one study only, 'curability in surgery' was shown to be a statistically significant and independent prognostic factor, whereas the local tumour extent, lymph node metastasis and lymphatic or vascular invasion were only significant in univariate analysis and not in multivariate analysis[18]. The present study shows that lymph node metastasis is the most important factor in tumour stage and, with venous invasion, significantly influences survival time. The relative risks are rather low. That distant metastasis was not significant for the prognosis can be explained by the fact that a distant metastasis is usually associated with advanced local disease, and prognosis has already been established by concomitant local complications of the carcinoma[2].

Tumour grade predicts the biological behaviour of many tumours[19], but in this study conventional tumour classification and grading did not predict outcome for patients with oesophageal carcinoma. A recent multifactorial study, however, showed the lymphocytic response to the tumour and vascular invasion to be significant[14]. Hambraeus *et al.*[17] developed a multiparameter histological grading system (including factors that express the tumour–host relationship, one of which is vascular invasion). They demonstrated its utility in multivariate analysis. Conventional tumour grading may be superseded by measurement of DNA content by flow cytometry[20]. Although not confirmed by all studies, some have shown that the DNA distribution pattern is a reproducible, statistically significant and independent prognostic factor in oesophageal carcinoma[16,21,22].

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Announcement

European Surgical Fellowships

Since 1990, the Council of *The British Journal of Surgery* has awarded European Fellowships, each holding a value of up to £3000. The first four successful applicants have now completed their Fellowships and Council has been pleased with the development of the scheme to date

Mr R. Graeme Wilson used the opportunity to visit European centres developing laparoscopic techniques Mr A. Ross Naylor used the opportunity to visit various vascular centres in Europe with particular reference to carotid artery surgery Mr Ashley Dennison used the opportunity to visit a specialist hepatobiliary unit in Switzerland. Mr Colin D. Johnson took the opportunity to visit centres in Germany with a special interest in hepatobiliary and pancreatic surgery

Three Fellowships have been awarded for 1991 to Mr B. J. Jenkins (London), Mr T. A. Lees (Newcastle-upon-Tyne) and Mr I. D. Anderson (Manchester).

Council are anxious to expand the scheme to allow surgeons working in other European countries to visit the UK. It is hoped that the candidates will use the Fellowships to visit surgical centres of their choice to extend their surgical experience. Fellowships will not be awarded solely for the purpose of attending courses or meetings.

It is Council's intention to offer European Fellowships once again in 1992. Applicants should submit details of their proposed itinerary and its anticipated costs, together with a curriculum vitae and two letters of support from senior colleagues. They should explain briefly how such a visit might broaden their experience and assist their career. Applications should be sent to the Company Secretary, Professor D. C. Carter, University Department of Surgery, Royal Infirmary, Edinburgh EH3 9YW by 31 January 1992

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The sphinctometer: a new device for measurement of lower oesophageal sphincter function

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Current evidence suggests that lower oesophageal sphincter (LOS) competence depends upon both pressure and length. Existing devices can measure length and pressure, but not simultaneously. This methodological problem is a fundamental drawback to understanding LOS function and its role in oesophageal disease. A 'sphinctometer' has been developed, consisting of an oil-filled 3-mm diameter Silastic chamber, 6 cm in length, incorporating a pressure microtransducer designed to provide an integrated pressure reading as a function of length. Its performance has been tested in vitro *using human cadaver oesophagus in a specially constructed chamber in which sphincter length and pressure can be varied independently. Comparisons were made with a conventional pull-through technique. Sphinctometer response was linear throughout the LOS pressure range of 0 to 50 mmHg at a fixed LOS length ($R_S = 0{\cdot}99$; $P < 0{\cdot}001$). Sphinctometer response was also linear at fixed LOS pressure for sphincter lengths from 1 to 6 cm ($R_S = 0{\cdot}99$, $P < 0{\cdot}001$). This device thus appeared suitable for monitoring function of the human LOS, and has subsequently been successfully incorporated into an ambulatory system for patient use.*

Lower oesophageal sphincter (LOS) function, especially the mechanisms by which it permits gastro-oesophageal reflux (GOR), is not well understood. A deficient resting tone is associated with excessive GOR and oesophagitis, but this is not the finding in all patients[1]. DeMeester *et al.* have proposed that the length of the LOS exposed to the positive pressure environment of the abdomen is also an integral component of the competency mechanism[2,3]. Transient, inappropriate LOS relaxation from a basal resting tone is an alternative mechanism by which GOR can occur[4], and has also been cited as an important event in the pathogenesis of reflux oesophagitis[5].

Measurement of LOS function is fraught with technical difficulties. Since LOS pressure has marked temporal variation[4], prolonged studies are a prerequisite. 'Point' sensors are inappropriate because the LOS makes orad excursions of up to 3 cm with movement and swallowing[6]. Only the Dent sleeve (with a sensing surface 6 cm long) is currently capable of long-term LOS pressure measurement, but this is a fluid-perfused device which is limited to the laboratory and requires the subject to be recumbent, thus restricting normal movement. It is also a unidirectional sensor and the LOS is markedly asymmetric in its pressure profile[7]. To obviate these problems, a solid-state, circumferentially sensitive 6 cm long sensing device has been developed which incorporates both the pressure and length components of sphincter competence

Patients and methods

The device (sphinctometer) consists of an oil-filled Silastic (Dow Corning, Reading, UK) cylinder 6·3 cm long and 3 mm in diameter, and contains a 4 mm long pressure microtransducer at its proximal end (*Figure 1*). Compression of the chamber is transmitted through the oil to the pressure sensor from which an electrical output is recorded Longitudinal Kevlar threads traverse the centre of the chamber to prevent stretch artifact. The chamber is mounted on a catheter of silicone rubber which can incorporate other sensors.

An artificial LOS was constructed in a test chamber (*Figure 2*). A length of cadaver oesophagus was secured between two hollow perspex rods inserted from both ends of the test chamber An LOS was simulated by the application of external hydrostatic pressure to the cadaver oesophagus from a reservoir (R), the length of the LOS could be varied by a movable stent. Internal chamber pressure was monitored by a pressure microtransducer (T) with a digital read-out (P) All test catheters were passed through the centre of the system, and pressure outputs were interfaced directly to a microcomputer, where they were recorded and analysed Pressure microtransducers were precalibrated and catheters were hydrated for 24 h and checked for drift All sphincter pressure measurements were obtained by standard station pull-through (SPT) manometry, where three pressure microtransducers mounted

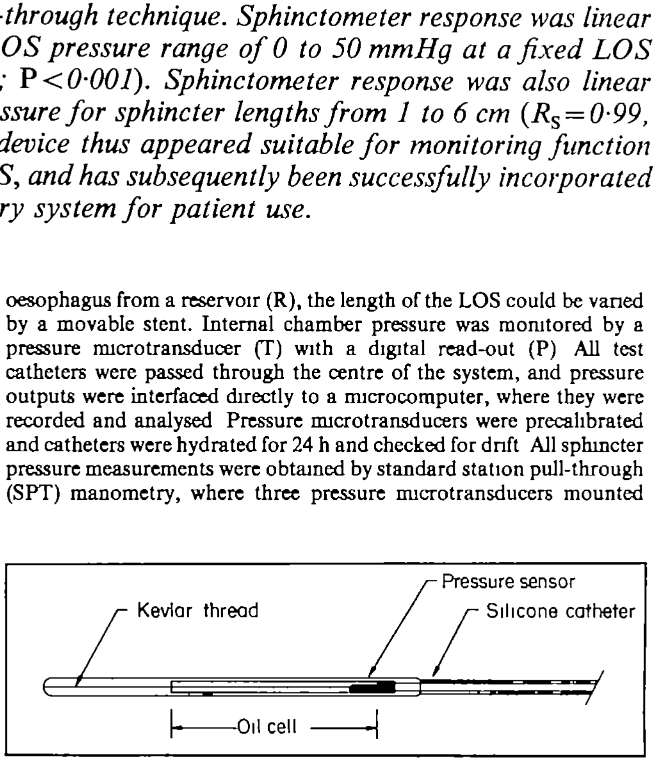

Figure 1 *Cross-section of the sphinctometer device. A 6·3 cm long oil-filled Silastic chamber contains a pressure microtransducer The Kevlar thread prevents stretch artifact*

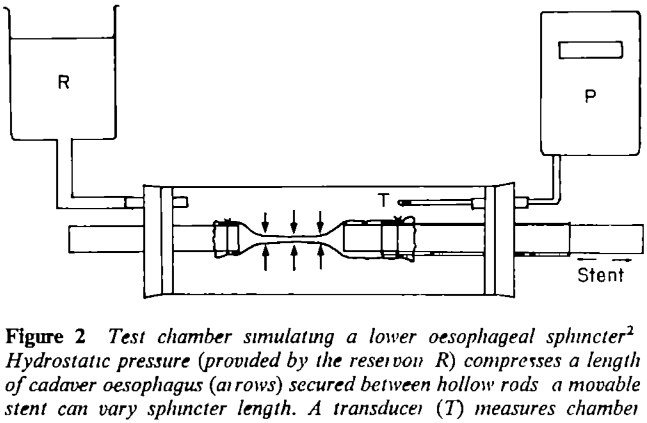

Figure 2 *Test chamber simulating a lower oesophageal sphincter[2] Hydrostatic pressure (provided by the reservoir R) compresses a length of cadaver oesophagus (arrows) secured between hollow rods a movable stent can vary sphincter length. A transducer (T) measures chamber pressure and gives a digital read-out (P)*

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on a catheter 5 cm apart and radially offset at 120° to each other were withdrawn through the sphincter and a mean of the three measurements recorded. Statistical analysis was by the Rank–Spearman correlation test.

Results

Two *in vitro* studies were carried out. In the first, sphinctometer output was measured as a function of sphincter length at a fixed sphincter pressure; in the second, sphincter pressure and sphinctometer output were correlated at a fixed sphincter length.

Study 1

At a sphincter length of 1 cm, the LOS pressure was adjusted to 10 mmHg and checked by SPT manometry. Sphincter length was adjusted from 1 to 6 cm and sphinctometer output was recorded. This was repeated at 10 mmHg pressure increments to 50 mmHg. The results (*Figure 3*) show that at each LOS pressure increment, the sphinctometer output is directly proportional to LOS length ($R_S = 0{\cdot}99$; $P < 0{\cdot}001$).

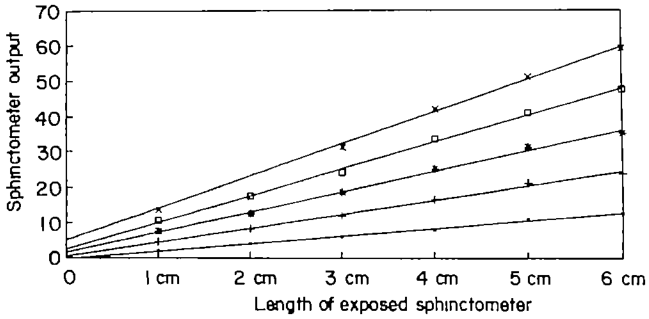

Figure 3 *Sphinctometer output as a function of sphincter length at a fixed sphincter pressure. —●—, 10 mmHg, —+—, 20 mmHg, —*—, 30 mmHg, —□—, 40 mmHg, —×—, 50 mmHg*

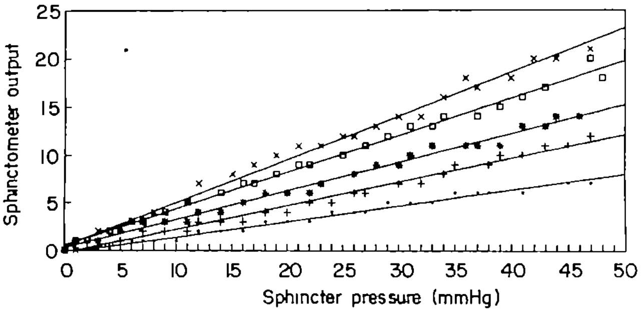

Figure 4 *Comparison of sphinctometer with sphincter pressure determined by station pull-through manometry at a fixed sphincter length Sphincter length —●—, 1 cm, —+—, 2 cm; —*—, 3 cm; —□—, 4 cm; —×—, 5 cm*

Study 2

Sphinctometer output was compared using SPT manometry at a fixed sphincter length. Test chamber pressure was increased in 2 mmHg increments from 0 to 50 mmHg, and, at each increment, the LOS was measured by SPT manometry and by the sphinctometer. This was repeated for LOS lengths from 1 to 5 cm. The results (*Figure 4*) show that sphinctometer output is directly proportional to LOS pressure ($R_s = 0{\cdot}99$; $P < 0{\cdot}001$).

In preliminary human studies, the sphinctometer was incorporated in a catheter system consisting of a gastric (P1) and three oesophageal body (P3, P4 and P5) transducers combined with a pH probe (Synectics, Medical Ltd, Enfield, UK) placed 5 cm above the top of the LOS. Recordings were obtained over 24 h by passing the catheter system via the anaesthetized nose into the oesophagus and linking up to a portable recording box. At the completion of the study the data was off-loaded onto a microcomputer for analysis. Sample traces of *in vivo* use of the sphinctometer in a normal subject and a patient with GOR are shown in *Figure 5*.

Discussion

In vitro results show that the sphinctometer device gives an output which is a linear relation of sphincter length and pressure, and thus functions as an integrator of the two components of sphincter competence which are currently considered to be important. LOS function has previously only been studied in stationary recumbent patients, and extrapolations to ambulant conditions are probably invalid because of the likely influence of movement and posture on LOS pressure and trans-sphincteric pressure gradients. The construction of the sphinctometer and its incorporation into a portable recording system has allowed prolonged LOS monitoring in ambulant subjects for the first time.

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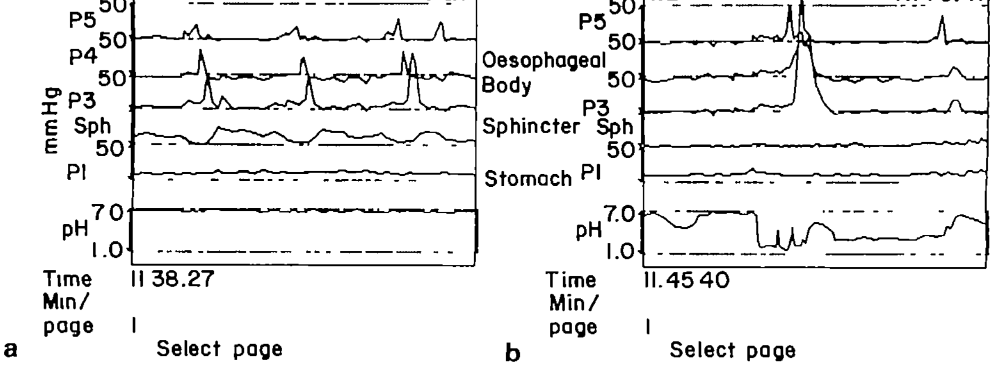

Figure 5 *Recordings from a normal subject* **a** *showing peristaltic waves with associated sphincter relaxation and a patient with GOR,* **b** *showing reflux events in the presence of low sphincter pressure. Sph: sphinctometer*

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Short note

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Outcome of stapled revision of retracted ileostomy

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The reported incidence of ileostomy retraction varies from 3 to 18·5 per cent[1–4]. It is believed to be a more common complication in obesity[5] and is associated with recurrent Crohn's disease[6]. Revision usually requires general anaesthesia, but recently a staple technique using intravenous sedation was described[7]. We have followed up ten patients who have undergone stapled revision of ileostomy for retraction to assess the outcome of this technique.

Patients and methods

Between 1988 and 1990 ten patients (nine women) with retraction of their end ileostomies underwent stapling with either a bladeless GIA® stapler or a TA 55® stapler (both US Surgical Corporation UK, Ascot, UK) Two to four rows of staples were inserted after eversion of the ileostomy with tissue forceps. In five patients the stapling was performed under general anaesthesia, but latterly it has been performed in outpatients without anaesthesia or sedation All patients were followed up and the immediate and long-term problems associated with the procedure were documented.

Results

The ileostomies had been present for between 2·5 and 33 years (median 10 years), and retraction had been a problem for between 1 month and 6 years (mean 38 months) (*Table 1*). In the patients with Crohn's disease the retraction was not associated with recurrent disease. The weight of the patients at the time of stapling was between 40 and 73 kg; no patient was overweight. The median follow-up period was 9 months (range 3–30 months).

In six patients the ileostomy became markedly swollen and oedematous after stapling; this settled spontaneously in all six patients One patient who had undergone stapling without anaesthesia complained that the procedure had been 'traumatic', but none complained of pain. Two of the group that had undergone general anaesthesia suffered slight pain after operation. Minimal bleeding occurred in four patients and stopped within 24 h in all patients. Outcome was not affected by the presence of oedema or bleeding after stapling. Six patients had no further retraction and no major problems associated with stapling. In four patients the procedure failed, requiring further surgery. In all four, retraction occurred within 1 month of stapling. Two patients developed sepsis after stapling, with a peristomal abscess causing obstruction in one patient This patient was an insulin-dependent diabetic who was receiving steroids. Another patient in whom the stapling was unsuccessful was also on steroids; none of the successful group was receiving steroids. The type of stapler used did not affect the outcome, and in those patients who have not had further surgery to the ileostomy the staples are still present and visible up to 25 months after the stapling. This can cause occasional bleeding during cleansing. There were no problems in the three patients with Crohn's disease, who have been followed for 3, 6 and 24 months.

Table 1 *Patient details and results of stapling*

Age	73	52 (male)	46	28	62	30	23	50	57	53
Diagnosis	Crohn's disease	UC	UC	Crohn's disease	Const.	Const.	Crohn's disease	FAP	UC	UC
Follow-up (months)	3	4	5	6	9	10	24	24	25	30
Stapler used	GIA	TA 55	GIA	GIA	TA 55	GIA	TA 55	TA 55	TA 55	GIA
General anaesthetic	+			+	+	+				+
Oedema		+	+	+	+		+			+
Bleeding			+	+	+	+				
Complications		Abscess	Ulceration					Sepsis		
Retraction		+				+		+		+
Medication		Insulin/ steroids								Steroids
Previous surgery			Refashioned 1985	Resited in past		Resited twice				

UC, Ulcerative colitis; FAP, familial adenomatous polyposis; Const., constipation/functional bowel disease

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Discussion

Stapling for retraction of an ileostomy is well tolerated, does not require anaesthesia, and can be performed in the outpatient department. Oedema often occurs after stapling, and patients should be warned of this. Two patients on long-term steroid therapy, including one diabetic, suffered complications and in such patients there may be a risk of sepsis. The procedure may be unsuccessful, with retraction recurring within 1 month; recurrence after standard refashioning has been reported to be about 20 per cent[8]. However, more than half our patients achieved a successful result from stapling, thus avoiding operative surgical intervention, and in these patients the effect is maintained. Crohn's disease is not a contraindication to stapling for retraction.

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Oxygenation in the stomach and the effect of truncal vagotomy

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A Clark polarographic oxygen electrode allowed detailed mapping of tissue oxygen ($P\text{to}_2$) *levels on the anterior surface of the stomach in five patients undergoing cholecystectomy. No significant difference in mean* $P\text{to}_2$ *was detectable between greater and lesser curvatures. A significant difference in mean* $P\text{to}_2$ *was detected between the body of the stomach and the pylorus (Mann–Whitney,* $P<0{\cdot}01$*). The effect of truncal vagotomy on* $P\text{to}_2$ *was evaluated in six patients undergoing this procedure for duodenal ulceration. Mean postvagotomy stomach* $P\text{to}_2$ *levels* (46 ± 12 *mmHg) were significantly lower (Wilcoxon test,* $P<0{\cdot}001$*) than prevagotomy levels* (59 ± 14 *mmHg). Truncal vagotomy did not have any significant effect on small intestinal* $P\text{to}_2$*. This work provides the first objective evidence of the relatively diminished tissue oxygenation in the gastric antrum and pyloric region, and confirms blood flow studies of the effects of vagotomy.*

It has been suspected for some time that gastric perfusion may be non-uniform in distribution. Early studies suggested that this had an anatomical basis, and Barlow *et al.*[1] demonstrated that the proportion of end arteries was much higher in the gastric antrum and duodenum than elsewhere in the stomach. Recent studies have demonstrated a higher proportion of end arteries along the lesser curvature of the stomach[2,3]. More sophisticated studies using radio-isotope clearance[4] and laser Doppler[5,6] techiques have demonstrated lower blood flows in the duodenum[4–6], lesser curvature[5] and antrum[6] compared to the remainder of the stomach. This may be a reason for the increased incidence of peptic ulcers in these areas.

The occurrence of gastrointestinal circulatory changes following truncal vagotomy has been well described[7–9], and involves reductions in blood flow of between 30·5 per cent[7] and 42 per cent[8]. It has been postulated that this reduction in blood flow may account for the cessation of bleeding following truncal vagotomy alone in upper gastrointestinal haemorrhage[7].

As $P\text{to}_2$ at any point is dependent on an adequate blood flow[10–12], decreased gastric blood flow should manifest as a decrease in gastric tissue oxygen tension. $P\text{to}_2$ levels can now be measured peroperatively from the serosal surface of the gastrointestinal tract in patients[12–15], using modified Clark-type polarographic oxygen electrodes (Cardiff Tissue Oximeter, University of Wales College of Medicine, Cardiff, UK) with highly reproducible results. This study, therefore, evaluates patterns of tissue oxygenation in the human stomach and examines the effect of truncal vagotomy.

Patients and methods

$P\text{to}_2$ was measured from consenting patients using a modified Clark-type polarographic oxygen electrode applied to the serosal surface of the gastrointestinal tract. This electrode, which has a linear response to oxygen, has been validated for clinical oxygen tension measurement and is unaffected by the anaesthetic gases used[14]. All patients were anaesthetized with halothane or nitrous oxide, without the use of anticholinergic premedication. Preliminary ethical approval was obtained for these studies.

Gastric tissue oxygenation

In the first part of the study, $P\text{to}_2$ levels were measured at predetermined sites on the stomach of five patients (mean age $42\pm7{\cdot}3$ years, range 32–49 years) undergoing cholecystectomy. Patients were maintained on an inspired oxygen concentration ($F\text{io}_2$) of 33 per cent and were closely monitored (central venous and intra-arterial) to ensure haemodynamic stability for the duration of the measurement period. The resultant mean arterial oxygen tension ($P\text{ao}_2$) was $145{\cdot}2\pm31{\cdot}1$ mmHg. $P\text{to}_2$ measurements were taken from a series of comparable points on the anterior surface of the stomach. Measurements were taken from the greater curvature, the lesser curvature and from a point midway between the two at the following five levels on the stomach: (1) pylorus, (2) midway between the pylorus and the incisura angularis; (3) the incisura angularis, (4) midway between the incisura angularis and the proximal body of the stomach; and (5) the proximal body of the stomach. Three readings were taken from each site and the $P\text{to}_2$ calculated from the mean of these.

Effect of truncal vagotomy

The effect of truncal vagotomy was evaluated in six patients undergoing this procedure for duodenal ulceration. The mean age of the patients was 44 ± 7 years (range 32–51 years), and patients were similarly maintained on an $F\text{io}_2$ of 33 per cent, resulting in a mean $P\text{ao}_2$ of $150{\cdot}6\pm33$ mmHg. Patients were monitored to ensure haemodynamic stability. $P\text{to}_2$ measurements were taken before vagotomy and pyloroplasty, and at least 5 min postvagotomy (but before pyloroplasty) from the same sites on the anterior surface of the stomach and from a small intestine control site.

Results were analysed by means of the Mann–Whitney and Wilcoxon tests, and Friedman analysis of variance, using the Microtab computerized statistical package (Acorn Computers Ltd, Cambridge, UK).

Results

Gastric tissue oxygenation

Although there was considerable variation in mean gastric $P\text{to}_2$ between patients (range 39–71 mmHg), measurements taken at the same site in individual patients were highly reproducible, with a variability averaging only $\pm1{\cdot}1$ mmHg. When the mean $P\text{to}_2$ of all greater curve ($56{\cdot}2\pm13{\cdot}6$ mmHg), lesser curve ($58{\cdot}7\pm10{\cdot}8$ mmHg), and anterior surface ($56{\cdot}1\pm11{\cdot}4$ mmHg) readings were compared, no significant difference in oxygenation was found.

The mean $P\text{to}_2$ (greater curve, lesser curve and anterior surface) of the pylorus, however ($53{\cdot}2\pm12{\cdot}9$ mmHg), was significantly lower (Mann–Whitney test, $P<0{\cdot}01$) than that of the body of the stomach ($62{\cdot}1\pm10{\cdot}1$ mmHg), and a gradual decrease in $P\text{to}_2$ was noted from proximal to distal stomach (Friedman test, $P<0{\cdot}025$) (*Figure 1*).

Effect of truncal vagotomy

The gastric $P\text{to}_2$ (mean of all observations) decreased by 22 per cent when measured 5 min after vagal transection (Wilcoxon test, $P<0{\cdot}01$) (*Figure 2*). There was no significant decrease in small intestinal $P\text{to}_2$ after this procedure (Wilcoxon test) (*Figure 3*).

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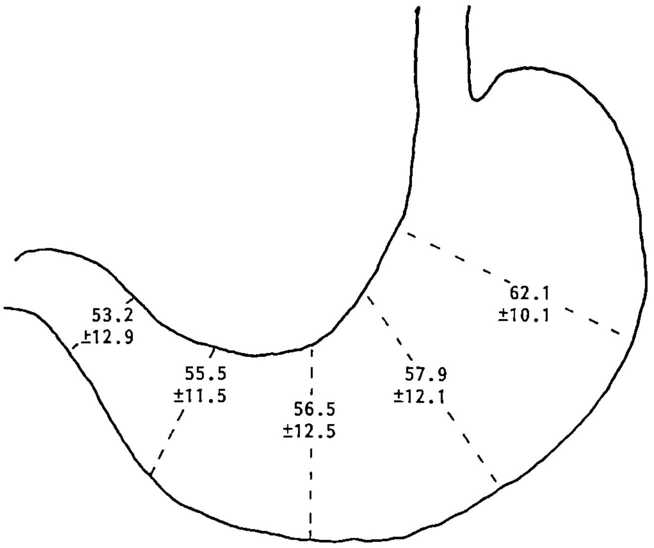

Figure 1 *Comparison of mean* Pto_2 *measurements at different levels on stomach.* ($P<0·01$ *Mann–Whitney test,* $P<0·025$ *Friedman test*)

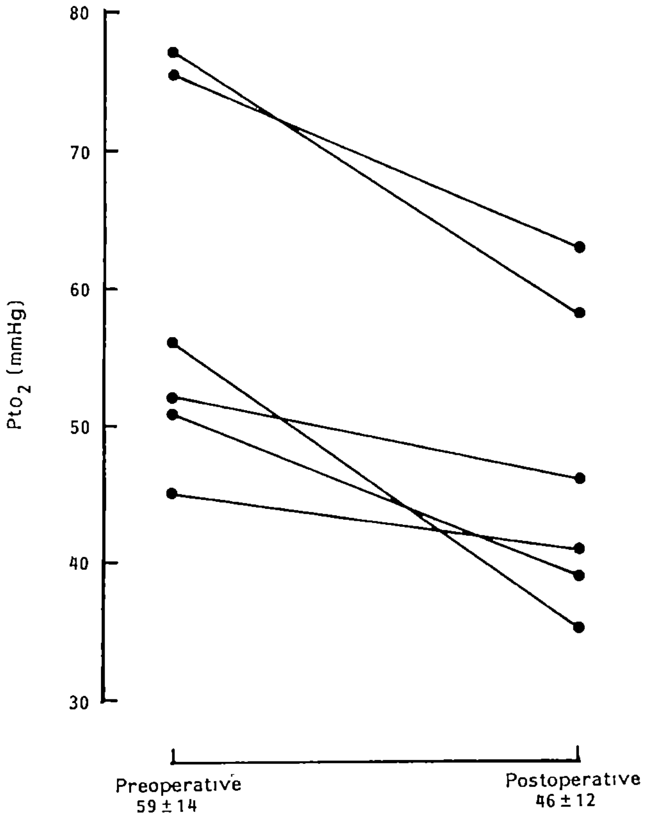

Figure 2 *Effect of truncal vagotomy on stomach* Pto_2 *levels* ($P<0·01$, *Wilcoxon test*)

Discussion

Gastric tissues are the most oxygenated in the gastrointestinal tract of animals[11] and man[12,13]. Locke *et al.*[11] found that the mean stomach $P\mathrm{to}_2$ in dogs was 63 ± 15 mmHg, compared to a mean small intestinal $P\mathrm{to}_2$ of 44 ± 11 mmHg. Similar differences were seen when gastric $P\mathrm{to}_2$ was compared with that of the small intestine (46·3 ± 15·4 mmHg *versus* 36 ± 9·7 mmHg, respectively) using the Cardiff Tissue Oximeter[12]. The reproducibility of $P\mathrm{to}_2$ readings using this technique is now established[12,15], and is confirmed in this study, the apparent large standard deviations in some of the results being due to interpatient variation in $P\mathrm{to}_2$.

Variations in tissue oxygenation within the stomach have not previously been reported. Recent studies have used the techniques of iodo-anti-pyrine clearance[4] and laser Doppler[5,6], and have demonstrated reduced antral and duodenal perfusion when compared with the rest of the stomach. The laser Doppler technique suggested that the lesser curve was less well perfused than the greater curve of the stomach[5]. This finding was not reproduced by Allen *et al.*[6], using similar equipment via an endoscope. The magnitude of the change in $P\mathrm{to}_2$ from proximal stomach to pylorus closely reflects the differences in blood flow demonstrated by Allan *et al.*[6].

Tissue oxygenation is a function of arterial blood flow, arterial oxygen tension ($P\mathrm{ao}_2$), and oxygen consumption. In fasting, anaesthetized patients, it is reasonable to assume that tissue oxygen consumption remains constant at a basal level. Since $P\mathrm{ao}_2$ remained constant during the studies, it is likely that differences in $P\mathrm{to}_2$ between sites represent variations in tissue blood flow.

Peptic ulceration may be localized to the antrum and duodenum because relative ischaemia may permit acid damage to the mucosal surface[1–6]. Although $P\mathrm{to}_2$ levels measured from the serosa may not represent those of the mucosal surface, the $P\mathrm{to}_2$ levels found within the 'ulcer bearing' areas in this study are well above those at which one would expect ischaemic damage to occur. Indeed, the critical $P\mathrm{to}_2$ for anastomotic healing in the colon has been shown to be in the region of 20 mmHg[13]. Intestine subject to experimental ischaemia has been shown to remain viable and histologically undamaged at $P\mathrm{to}_2$ levels well below this[15]. Studies examining stress ulceration in rats have shown that such ulcers frequently occur outside the classical ulcer bearing areas but do not become evident until prolonged exposure to marked hypoxia and hypoxaemia ($P\mathrm{ao}_2$ of 27 mmHg or less[16]), at which level one would expect the gastric $P\mathrm{to}_2$ to be of the order of 10 mmHg[12].

Intestinal mobilization with an intact blood supply does not affect local tissue oxygenation[14] and this could not be

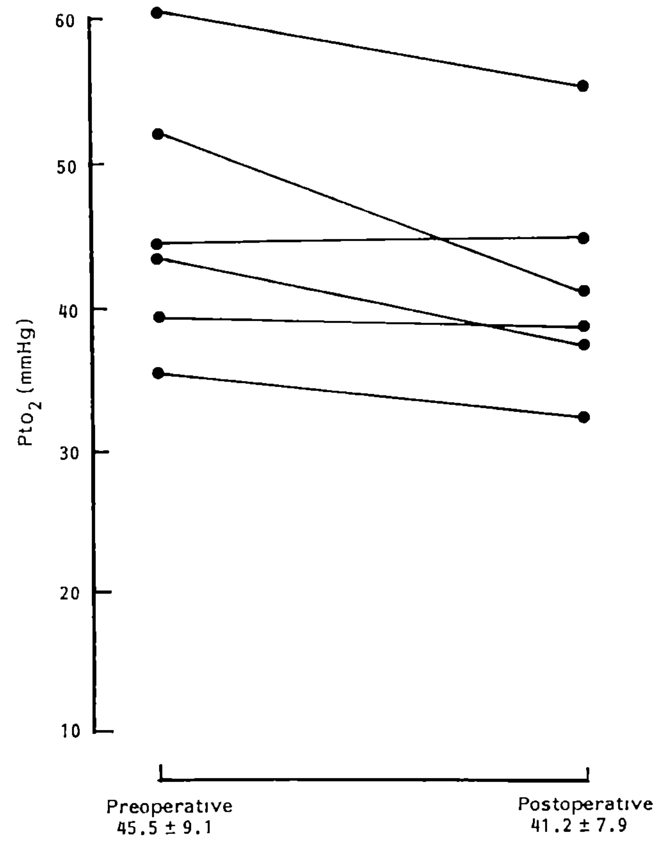

Figure 3 *Effect of truncal vagotomy on small intestinal* Pto_2 *levels (not significant, Wilcoxon test)*

responsible for the changes observed after vagotomy. This study demonstrates that truncal vagotomy is associated with a significant decrease in gastric tissue oxygenation of 22 per cent (*Figure 2*), a finding similar to that noted by Peter *et al.*[7], who recorded a 30·5 per cent reduction in canine gastric blood flow after truncal vagotomy. The reason is unclear but may represent the vasoconstrictive effect of unopposed sympathetic activity[8,9] If relative ischaemia was a cause of peptic ulceration, then truncal vagotomy should exacerbate the problem. The findings support the theory that vagotomy achieves its beneficial effect by reducing gastric blood flow, as reflected by reduced tissue oxygenation, with a resultant decrease in gastric secretion[7].

Acknowledgement

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Recurrent peptic ulceration after highly selective vagotomy: long-term outcome

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A prospective assessment was made of the outcome 4 years after diagnosis of recurrence in a group of 27 patients with documented ulceration after highly selective vagotomy (16 symptomatic recurrence and 11 asymptomatic). In the 16 patients with a previous symptomatic recurrence, eight of the 11 patients with duodenal ulcer underwent a further endoscopy at 4 years and one active ulcer was found. Five patients with previous symptomatic gastric ulcer recurrence have all undergone further surgery. In the 11 patients who originally had an asymptomatic ulcer recurrence (five gastric, six duodenal) no patient has undergone further surgery, although two patients with a recurrent gastric ulcer and two with a recurrent duodenal ulcer subsequently developed symptoms from their ulcer and required H_2 receptor blocker therapy. Eight of the 11 originally asymptomatic patients underwent further endoscopy at 4 years and two further duodenal ulcers were found. After highly selective vagotomy, asymptomatic ulcer recurrence occurs frequently and 40 per cent of these patients may develop symptoms.

This study examines the natural history of ulcer recurrence in patients who have undergone highly selective vagotomy (HSV) The presence of symptomatic and asymptomatic ulcer recurrence after HSV has been reported previously[1]. In that study a 9 per cent symptomatic recurrence rate and a 9 per cent asymptomatic recurrence rate confirmed by endoscopy were demonstrated. Long-term outcome for these patients was not determined. Follow-up was therefore conducted 4 years after the original assessment of ulcer recurrence to identify ulcers that pose specific risks. The implication of ulcer site and recurrence in long-term management of such patients was determined.

Patients and methods

Patients

Originally 174 consecutive patients were studied (median age 45 years, range 19–75 years). All had HSV performed or supervised by one of two surgeons (R.B.J., G G.J.). There were 129 men (74 per cent) and 45 women (26 per cent). Subsequent review of the medical history in the group showed that 16 recurrences (9 per cent) had been documented From the remaining group of asymptomatic patients, 119 agreed to be re-endoscoped and a further 11 (9 per cent) patients were found to have ulcer recurrence In the symptomatic group five had gastric ulcers and 11 duodenal ulcers. The asymptomatic group had five patients with gastric ulcers and six with duodenal ulcers.

Follow-up

Four years after the conclusion of the original study (and a minimum of 7·5 years after HSV) a further follow-up was made of the outcome in this group of 27 patients. Details of their medical history were ascertained, including whether further operation had been required, whether symptoms had persisted or developed, whether treatment had been or was to be instituted, and whether any complications had supervened. All patients were invited to undergo repeat endoscopy. It was made clear that this did not represent a necessary part of their treatment or postoperative care but that they would be advised of the results obtained.

Results

Symptomatic ulcer group

There were 16 patients in this group (ten men, six women, median age 54 years, range 28–67 years). In the five patients with gastric ulcer, all had had further surgery (four gastric resection, one vagotomy and drainage). The decision for surgery was taken by a surgeon outside this group of authors. One patient had the Zollinger–Ellison syndrome and has been excluded from further analysis. Eight of the remaining ten patients agreed to undergo endoscopy and one was found to have an active duodenal ulcer. Seven of the ten patients available for follow-up were still receiving regular treatment with H_2 receptor blockers. The three not receiving treatment were asymptomatic.

Asymptomatic ulcer group

There were 11 patients in this group (seven men, four women, median age 46 years, range 20–69 years). None of this group had undergone further surgery. Two patients with gastric and two with duodenal ulcers eventually developed symptoms and were given treatment with H_2 receptor blockers.

In this group eight patients agreed to endoscopy after 4 years and two duodenal ulcers were found. One ulcer was found in a patient who had remained asymptomatic throughout the period of review and the other was found in a patient who had become symptomatic but had not sought treatment.

Repeat endoscopy group

There were 16 patients who had not undergone further surgery and who had a further endoscopy approximately 4 years after the original study. In this group no new recurrent gastric ulcers were found. Duodenal ulcers, however, persisted in three patients.

Discussion

Although specifically addressing the question of asymptomatic peptic ulcers after surgery, this study further highlights the importance of symptomatic ulcer recurrence after HSV. The rate of symptomatic ulcer recurrence reported varies with the period of follow-up[1–10] and the expertise of the surgeon performing the surgery[7,8]. Few studies have follow-up in excess of 5 years. Those with follow-up between 5 and 12 years report incidences of 10–25 per cent in a total of 1258 patients[11] with 5 year recurrence rates varying widely from 1 per cent[12] to over 15 per cent[9].

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Our group of patients initially had a median follow-up of 36 months (range 3–94 months) with a 9 per cent symptomatic recurrence rate[1].

When followed for a period greater than 10 years, ulcer recurrence rates between 7 and 38 per cent[8,10] have been reported.

Recurrent symptomatic ulceration after HSV is found to be gastric in about one-third of patients[1,10]. The finding of symptomatic gastric ulcers in five patients of our symptomatic recurrent ulcer group led to all patients having further major gastric surgery although the patients were neither assessed nor operated on by the authors. Nevertheless, this suggests that the ulcer diathesis present in these patients was not adequately treated by HSV alone. Asymptomatic ulcer recurrence after HSV has been less well studied. Some reports suggest incidences of asymptomatic ulcers equal to that of symptomatic ulcers[1,13,14]. Patients who are well are likely to be reluctant to undergo another endoscopy to permit documentation of possible asymptomatic ulcers. What is the significance of an asymptomatic ulcer diagnosed in a patient after HSV? Are such ulcers trivial and to be ignored or are they an early warning of later symptomatic disease?

In our patients, asymptomatic ulcers were not associated with subsequent surgery. However, four of 11 patients ultimately developed symptoms and received H_2 receptor blocker treatment. Of the eight symptomatic patients re-endoscoped at 4 years, only one patient was found to have an active ulcer present despite being managed on H_2 receptor blocker treatment. This suggests that asymptomatic peptic ulcers developing after HSV may be a less aggressive form of ulcer recurrence than symptomatic disease after HSV. If a patient is noted to have an asymptomatic ulcer after HSV, assurance can be given that major complications of the disease are unlikely. Of particular note were the five patients with asymptomatic gastric ulceration. No additional surgery was required in these patients although two had treatment with H_2 receptor blockers, which produced complete healing. This contrasts with the patients with symptomatic gastric ulcer recurrence, all of whom had further surgery. The aetiology of such gastric ulceration after HSV is not clear. When asymptomatic initially, however, gastric ulceration does seem to follow a benign course. The gastric ulceration in these patients may be related to lesser curve ischaemia[15], in which case healing with time would be expected and may have occurred. The degree of ischaemia may be greater in symptomatic patients.

With the exception of the group with symptomatic gastric ulcers, the remaining patients with ulcer recurrence responded rapidly to maintenance therapy with H_2 receptor blockers. This suggests that HSV produces less aggressive ulcer disease. This observation has been made by others[2–5]. It may not be sufficient to analyse ulcer recurrence rates alone to ascertain the efficacy of surgery. It may be more appropriate to analyse the mortality rate and morbidity of the operative procedure, its ulcer recurrence rate and the ease with which symptomatic recurrence can be treated by conventional medical treatment.

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The modified AFP score: an attempt to make the results of anti-reflux surgery comparable

Comparison of different strategies in anti-reflux therapy is complicated by wide variations in patient selection and in the criteria employed to assess outcome. A modification of the classification system originally developed by Bancewicz et al.[1] *was used to grade a series of 57 patients before and after fundoplication (primary reflux group). An additional group of 39 patients with an unsatisfactory result after previous Nissen fundoplication (failed Nissen group) were assessed before and after reoperation. The classification system used comprises three elements: the A element depicts gastro-oesophageal anatomy based on the findings at endoscopy: the F element codes the amount of acid reflux by means of 24-h intra-oesophageal pH monitoring; and the P element describes mucosal abnormalities. The overall severity was quantified by means of a score on a scale from 0 to 10. The mean preoperative score in the primary reflux group was 5·45 and in the failed Nissen group 7·3. After fundoplication, this was reduced to 1·07 and 1·30, respectively. In general, there was good correlation between the results of the three elements under consideration, pointing to a potential pathophysiological inter-relationship. Marked individual variation did occasionally occur. The AFP system enabled a detailed description of the preoperative and postoperative condition of the patient, and proved easy to use in clinical practice. Its employment is recommended as an objective means of comparing the value of different treatment strategies.*

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The results of medical and surgical strategies employed in the management of gastro-oesophageal reflux disease are difficult to compare because of wide differences in patient selection. It is generally agreed that therapeutic success depends on disease severity. Accordingly, many attempts have been made to define precisely the degree of abnormality before treatment. Objective tests such as pH monitoring (amount of acid reflux), manometry (functional disturbances) or endoscopy (presence of oesophagitis) have been used. Experience, however, has shown that these unidimensional parameters are insufficient to characterize an individual patient's disease exactly.

The importance of a precise classification before treatment has long been recognized in oncological practice. The TNM system offers a reliable means of staging the tumour and enables different therapeutic manoeuvres to be compared. Bancewicz *et al.*[1] approached the problem of grading gastro-oesophageal reflux disease in a similar manner. They developed a simple classification which can be used to assess the outcome of anti-reflux surgery in different patients with varying degrees of disease. This method was used in two separate surgical units, and its value in clinical practice proved. Furthermore, the authors demonstrated major differences between the patient populations and in the indications for surgical treatment.

We adopted this classification system, but found that it benefited from modification for three reasons. Firstly, many units no longer routinely perform barium radiology, but instead rely solely on endoscopy. Secondly, the classification of oesophagitis as used by the authors is not as comprehensive or as widely accepted as that described by Savary and Miller[2,3]. Thirdly, the original grading system does not allow for a clear definition of the situation after surgery

The aim of the present study was to apply a modified classification, before and after surgical treatment, to a consecutive series of patients to test its applicability.

Methods

Reflux disease grading

The classification system suggested by Bancewicz *et al.*[1] includes anatomical, functional and pathological aspects as a means of grading the findings in patients with gastro-oesophageal reflux disease. The letter 'A', denoting anatomy, is used to describe the presence and type of hiatal hernia; the letter 'F', denoting function, codes the findings on 24-h intra-oesophageal pH testing; and 'P', denoting pathology, depicts the presence of mucosal lesions as seen at endoscopy (*Table 1*). Each of these three elements is graded according to severity.

Using our modifications, both the A and F elements were given one of four grades.

Since our interpretation of the A element was based on endoscopic findings, the following definition was used.

Grade 0, no hernia present
Grade 1, small hernia present
Grade 2, large hiatal hernia present
Grade 3, mixed sliding and para-oesophageal hernia, or para-oesophageal hernia alone.

Oesophageal function (F) is determined by 24-h pH monitoring according to standard criteria as established by Johnson and DeMeester[4].

Grade 0, no pathological reflux
Grade 1, reflux related to meals
Grade 2, reflux in the fasting state
Grade 3, spine (nocturnal) reflux with or without upright reflux

The P element is subdivided into five classes, based on the original description of Savary and Miller[2,5].

Grade 0, no macroscopic mucosal abnormalities
Grade 1, macroscopic oesophagitis consisting of isolated lesions in the distal oesophagus, either with or without the presence of superficial necroses
Grade 2, linear longitudinal lesions in the distal oesophagus, either with or without superficial necroses

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Table 1 *Original AFP classification of gastro-oesophageal reflux disease according to Bancewicz* et al.[1]

A, Anatomy	
Group 0	No hiatal hernia on routine radiology (no provocative manoeuvres) or endoscopy
Group 1	Sliding hiatal hernia which reduced on screening or spot film radiology
Group 2	Sliding hiatal hernia which was not seen to reduce on screening or spot films
Group 3	Mixed sliding and para-oesophageal hernia or pure para-oesophageal hernia
F, Function (pH assessment)	
Group 0	No pathological reflux on 24-h pH testing
Group 1	Reflux related to meals
Group 2	Upright reflux not related to meals
Group 3	Supine reflux with or without upright reflux
(The letters L (low), N (normal), or H (high) can be added to the code in this section to denote diminished, normal or increased pressures in the body of the oesophagus on manometry)	
P, Pathology	
Group 0	No macroscopic mucosal abnormality
Group 1	Macroscopic oesophagitis consisting of at least linear streaks in the distal oesophagus
Group 2	Concentric fibrosis (stricture)
Group 3	Longitudinal fibrosis (short oesophagus) or penetrating ulcer
(The letters CLO can be added to the code in this section to indicate the presence of a columnar-lined oesophagus. PS may denote previous surgery.)	

Grade 3, confluent, circular oesophagitis
Grade 4, complicated reflux oesophagitis (penetrating ulcers, strictures, longitudinal fibrosis).

In this classification system, the presence or absence of a Barrett oesophagus was not taken into consideration, since a columnar lined oesophagus is considered *per se* to be a scar resulting from chronic reflux oesophagitis. However, this finding can be indicated for the sake of completeness by adding the letters CLO (columnar lined oesophagus) to the respective pathological grade.

Postsurgical grading

The postsurgical anatomy (A_{PS}) is described as follows·

A_{PS} Group 0, proper localization of the fundic wrap
A_{PS} Group 1, epidiaphragmatic position of the wrap
A_{PS} Group 2, cuff disruption
A_{PS} Group 3, cuff too low in relation to the lower oesophageal sphincter, or slippage of the cuff
A_{PS} Group 4, cuff too tight.

Although this classification is intended to describe the situation after fundoplication, it can easily be adapted for use after other anti-reflux procedures. The F and P elements are used in the same way as before surgery.

Patients

A total of 57 patients with primary reflux disease (primary reflux group) and 39 patients with an unsatisfactory result after previous fundoplication (failed Nissen group) were examined before and after anti-reflux surgery.

Primary reflux group

A consecutive series of 57 patients with primary reflux disease who had undergone surgery between 1986 and 1989 were examined before and after fundoplication. The median age was 52·3 years (range 15–82 years) and the sex ratio was 66 per cent men:34 per cent women. The median age was lower in men (50 years, range 15–77 years) in comparison to women (median 57·4 years, range 22–82 years) The operative procedure in each case was strictly standardized using a previously described modification of the Nissen–Rossetti fundoplication[6]. Particular attention was paid to the construction of a short floppy fundoplication. All patients were assessed after surgery at between 3 and 17 months (median 13 months)

'Failed Nissen group'

A consecutive series of 39 patients were referred for reoperation from 1983 to 1989 after previously unsuccessful fundoplication The sex ratio was 29 men:10 women, with a median age of 50·9 years (range 30–70 years). The median age in men was slightly lower (48·9 years) compared with that in women (50·05) In all patients, refundoplication was performed via an abdominal approach[7].

Results

Primary reflux group

Anatomy (*A*). Before surgery, 21 per cent of patients had no hiatal hernia, while a similar percentage had a small hiatal hernia. Of the remainder, 47 per cent had a large hiatal hernia and 11 per cent had either a mixed para-oesophageal hernia or a para-oesophageal hernia alone.

After surgery, the relationship had changed dramatically· 85 per cent were now classified as A_{PS} Group 0, one patient (1·7 per cent) as A_{PS} Group 1, four patients (7 per cent) as A_{PS} Group 2, and the final patient (1·7 per cent) as A_{PS} Group 3. None was classified as A_{PS} Group 4.

Function (*F*). Before surgery, 23 per cent of patients had no pathological reflux, and, in a similar percentage, reflux was only related to meals. In the remainder, pathological reflux occurred in the fasting state in 3 per cent and in the supine position in 51 per cent.

After surgery, 44 patients (77 per cent) fulfilled the criteria for F_0, six patients (11 per cent) were F_1, four patients (7 per cent) were F_2, and three patients (5 per cent) were F_3.

Pathology (*P*). Endoscopic examination revealed that 16 per cent of patients did not have any signs of reflux oesophagitis before surgery, 9 per cent belonged to Group 1, 38 per cent to Group 2, 18 per cent to Group 3, and 19 per cent to Group 4.

After surgery, 44 patients (77 per cent) did not demonstrate any oesophagitis, three patients (5 per cent) had Grade 1 oesophagitis, seven patients (12 per cent) had Grade 2 oesophagitis, and three (5 per cent) had Grade 4 oesophagitis.

The preoperative and postoperative AFP distribution is shown in *Figure 1*.

Failed Nissen group

Anatomy (*A*). Before surgery, 15 per cent of patients had a supradiaphragmatic hernia, 18 per cent an open cuff, and 67 per cent had an abnormally low or slipped cuff None of the patients in this study had a cuff which was considered too tight.

After operation, 82 per cent of patients had a normal anatomy, 12 per cent were graded A_1, and 6 per cent were A_3. None of our patients was graded A_4.

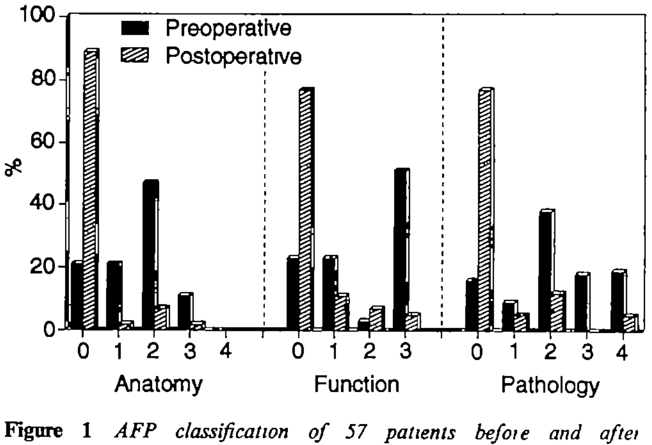

Figure 1 *AFP classification of 57 patients before and after fundoplication*

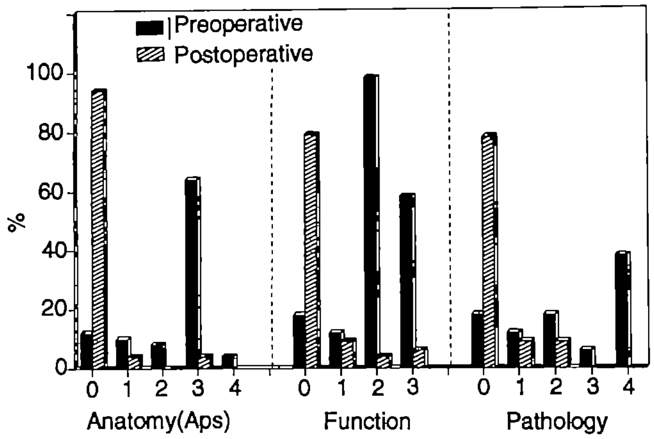

Figure 2 *AFP classification of 39 patients with a failed Nissen before and after refundoplication*

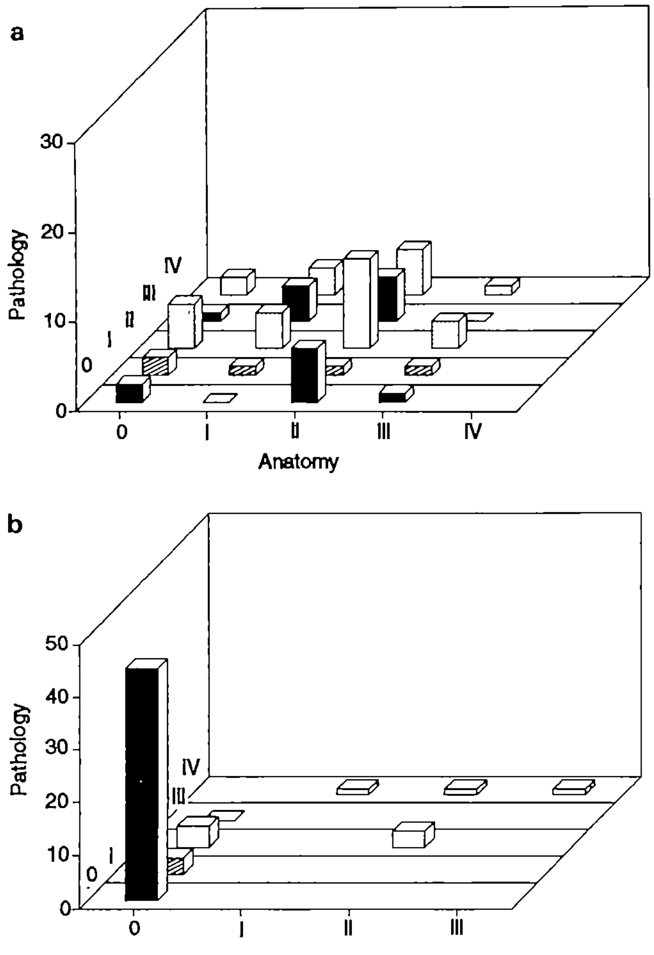

Figure 3 *Inter-relationship between pathology and anatomy in 57 patients* **a** *before operation,* **b** *postoperatively*

Function (*F*). Before operation, 17 per cent of patients did not demonstrate any pathological reflux, 23 per cent had only postprandial reflux, 9 per cent had reflux in the fasting state, and 51 per cent in the supine position.

After surgery, function was normal in 70 per cent, 10 per cent were graded as F_1, and 20 per cent were graded as F_2.

Pathology (*P*). In 13 per cent of patients, there was no evidence of endoscopic oesophagitis before surgery Grade 1 oesophagitis was found in 16 per cent, Grade 2 in 26 per cent, whereas Grade 3 oesophagitis was present in 5 per cent and Grade 4 oesophagitis was detected in 39 per cent.

After surgery, no mucosal lesions were seen in 82 per cent of patients, whilst the remaining 18 per cent demonstrated Grade 2 reflux oesophagitis.

Figure 2 shows the $A_{Ps}FP$ distribution before and after reoperation.

Interdependence of the AFP elements

If all AFP subgroups are considered, a total of more than 70 possible combinations (from $A_0F_0P_0$ to $A_3F_3P_3$) can be calculated. To compare like with like, this would require large numbers of patients, who are difficult to obtain in any centre. Additionally, a long list of subgroups is difficult to perceive and to interpret. A more practical approach is the use of a three-dimensional plot of the respective elements.

Figure 3 illustrates the correlation between anatomy and pathology. It can be seen that a clear relationship exists between the size of the hiatal hernia and the extent of the mucosal lesions before operation (*Figure 3a*). After fundoplication it is evident that both pathological and anatomical abnormalities have been successfully corrected (*Figure 3b*).

The interdependence of both function and pathology has previously been reported[4]. This finding was again confirmed in our patients (*Figure 4a*). *Figure 4b* shows that both parameters were equally improved by surgery.

A more surprising finding was that the size of the hiatal hernia and the degree of gastro-oesophageal reflux appear to be related (*Figure 4*). It would, therefore, seem that fundoplication leads to a normalization of both anatomy and gastro-oesophageal reflux.

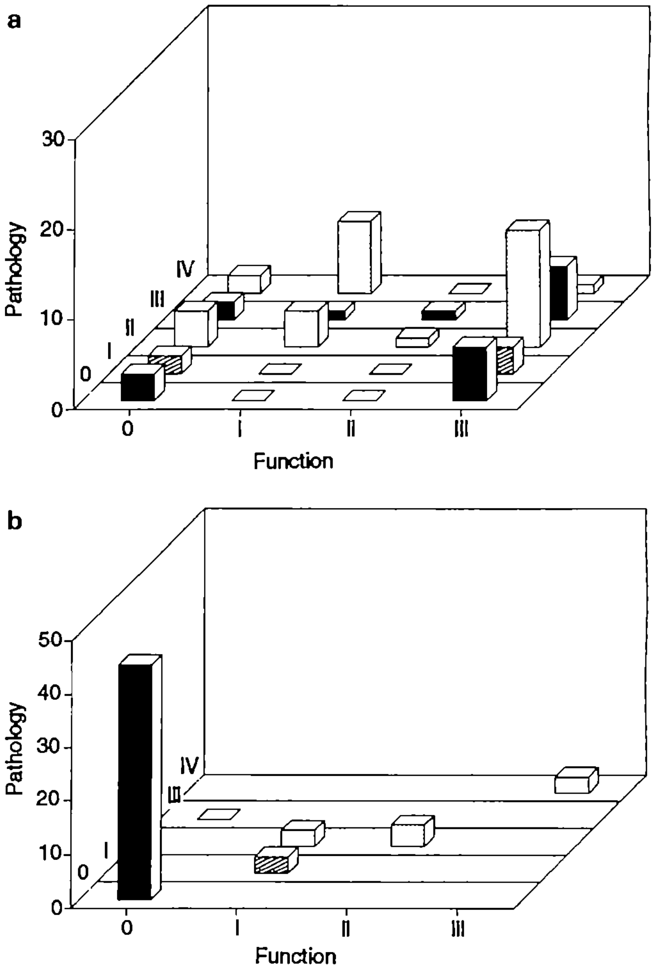

Figure 4 *Inter-relationship between pathology and function in 57 patients* **a** *before operation,* **b** *postoperatively*

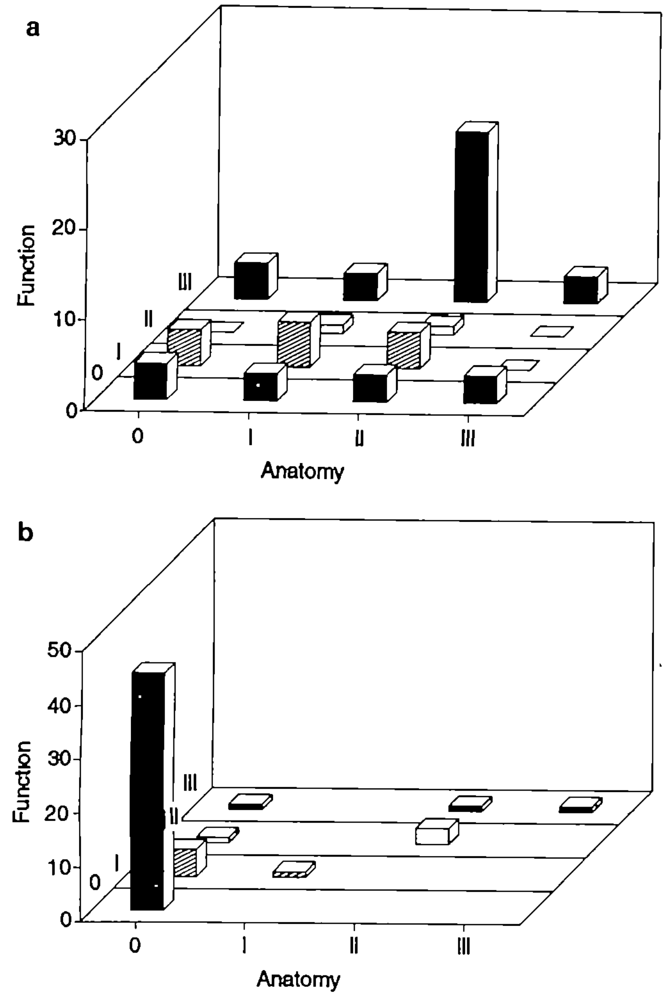

Figure 5 *Inter-relationship between function and anatomy in 57 patients* **a** *before operation*, **b** *postoperatively*.

AFP score

To facilitate the comparison of different types of patients and to quantify the operative result, a score was developed. If we assume that all elements of the AFP system are of equal rank, it is possible to give each patient's disease a numerical value based on the sum of the respective elements (AFP_0 being the best and AFP_{10} describing the worst situation).

This score can be calculated for individual patients as well as for the respective cohort according to the formula $A+F+P/n$, where n is the number of patients and A, F, P the respective elements graded according to severity

In this study, patients with primary reflux disease had a mean AFP score of 5·45 before fundoplication, which fell after operation to 1·22

In patients with a failed Nissen fundoplication the mean A_{PS}FP value before surgery was 7·3, and subsequently fell to 1·07 (*Figure 6*).

Discussion

The AFP classification of gastro-oesophageal reflux disease, originally suggested by Bancewiecz *et al*[1], is an important piece of work which deserves wide attention. There are many reports in the literature of medical and surgical measures which are claimed to be of benefit in the treatment of this disease. Unfortunately, comparison is difficult as frequently only one or two reflux parameters, such as endoscopy or pH monitoring, are used to measure success. We therefore do not know clearly the situation before and after therapy. The AFP classification is the first attempt at a universally applicable and comprehensive means of assessment in reflux disease.

In clinical practice, the AFP classification proved easy to use. Each physician dealing with a particular patient had a clear idea of the state of his or her disease. Experience showed, however, that the original classification benefited from a degree of modification. Many units now rely solely on the results of endoscopy. The use of the Savary and Miller classification of oesophagitis also proved to be more comprehensive and universally acceptable[2,5,6]. Finally, a clear definition of the situation after surgery proved valuable in patients with an unsatisfactory result after previous fundoplication.

The inclusion of the results of endoscopy and pH monitoring in the classification system developed by Bancewicz *et al.*[1] is logical What is controversial is the addition of the third element, namely the presence and state of any hiatal hernia. Herniation was considered important in the 1950s Oesophageal surgeons such as Allison, Belsey and Nissen designed operations with the sole aim of correcting this abnormality. From the work of Bombeck *et al.*[8] and Palmer[9] came the idea that the presence of a hiatal hernia was unimportant in the pathogenesis of gastro-oesophageal reflux disease. The results of our study point to a correlation between the presence and size of a hiatal hernia and degree of reflux, and support its inclusion in a classification such as this

It can be argued that the correlation between the results of the various elements involved in the AFP system make it unnecessary to include all three; one representative parameter might be enough. Unfortunately, individual variation means that this is not the case. Approximately one-fifth of our patients had evidence of gastro-oesophageal reflux on pH monitoring, but no evidence of oesophagitis at endoscopy. The additional use of an element which depicts the anatomical situation before surgery is essential since the presence of a large hiatal hernia might influence the technical difficulties of the operation The results of pH monitoring or the presence of oesophagitis at endoscopy do not give this information. Therefore, all three elements need to be included to give a complete picture.

The use of a cumulative score is simple and convenient, and gives an indication of the severity of the patient's disease. Unfortunately, important facts remain hidden, e.g. the presence of a large hiatal hernia. Whether each element can be given equal weight is at present unknown and requires further study.

The AFP classification is analogous to the TNM system used in oncology. The question therefore arises whether this system has any prognostic value. In our patients, the severity of the preoperative condition had no apparent influence upon the postoperative outcome. The mean preoperative scores of 5·45 and 7·3 in the primary reflux group and the failed Nissen group, respectively, shows clearly the disease severity. The postoperative scores were significantly reduced, to 1·07 and 1·3, respectively, suggesting that the condition can be successfully 'cured' (at least in the short term), no matter how severe it is. This finding is contrary to that generally found in the treatment of cancer patients. If the results of fundoplication are so good it might be argued that it is unnecessary to assess patients so carefully after treatment. This statement can only be made on

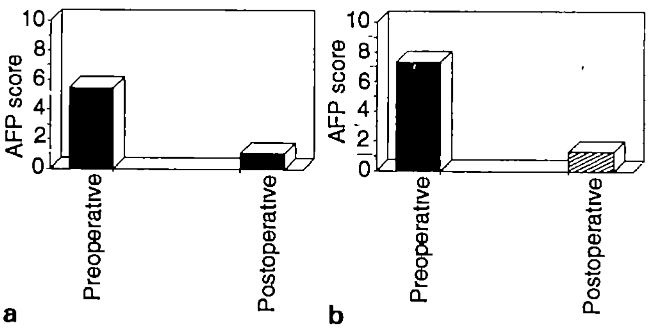

Figure 6 *Comparison of AFP scores before and after* **a** *primary fundoplication and* **b** *refundoplication*

the basis of more information about other techniques from other centres, and therefore the need for clear assessment in each case remains.

The classification system is open to two further areas of criticism. What matters most to the patient is his or her symptoms. This is not taken into account in the AFP classification. It is widely known that the correlation between symptoms and objective tests of gastro-oesophageal reflux is often poor. However, it is very difficult to assess objectively subjective symptoms and, therefore, this should be better left to specialized life studies. For practical purposes, the classification system would appear to be sufficient as it stands.

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Endoscopic balloon tamponade of iatrogenic bleeding from oesophageal varices

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Sclerotherapy of oesophageal varices via a fibreoptic endoscope is well established[1]. Variceal haemorrhage is initially controlled by balloon tamponade, which may be left *in situ* for sclerotherapy[1]. Alternative means of controlling haemorrhage during sclerotherapy include use of a rigid oesophagoscope, an endoscopic sleeve[2] or an inflatable cuff on the endoscope tip[3] Electively, variceal sclerotherapy is often performed 'freehand' without the use of balloon tamponade. Minor haemorrhage is controlled by local pressure to the varix with the endoscope tip. Failure to control haemorrhage necessitates insertion of a Sengstaken balloon and admission to hospital. We describe a new technique for achieving haemostasis after freehand sclerotherapy which is simple, effective and well tolerated. Two patients recently underwent elective injection sclerotherapy of oesophageal varices. Both had a history of cirrhosis and both had previously been treated for variceal haemorrhage. Neither patient was bleeding at the time of the examination. After sedation with intravenous midazolam and pethidine, intravariceal injection was performed with a 23-gauge sclerotherapy needle (Microvasive 1123, Watertown, Massachusetts, USA) using ethanolamine oleate via the Olympus XQ20 endoscope. The injections were performed at the gastro-oesophageal junction. Haemorrhage occurred following injection, and this persisted despite both reinjection and the use of direct pressure with the tip of the endoscope An 18 mm diameter balloon (Microvasive Rigiflex) was inserted down the endoscope and placed at the gastro-oesophageal junction. The balloon was inflated to 35 psi (241 kPa) and held in place, under direct vision, for 4 min. In both cases the haemorrhage ceased and no further sedation or analgesia was required. The patients did not require insertion of an uncomfortable balloon tube and both were able to return home following the procedure

We feel that this simple and effective technique would be a useful addition to the armamentarium of the endoscopist.

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Laparoscopic ligamentum teres (round ligament) cardiopexy

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A technique of laparoscopic ligamentum teres cardiopexy for reflux oesophagitis unresponsive to medical treatment is described. The procedure has been performed on five patients and on postoperative testing has been shown to achieve competence of the lower oesophageal sphincter by lengthening of the intra-abdominal segment, accentuation of the angle of His and elevation of the pressure in the high pressure zone. All the patients have been relieved of their symptoms by the operation and have not sustained any adverse effects but the follow-up period is short.

Oesophageal reflux disease is one of the commonest disorders of the gastrointestinal tract. Treatment with histamine H_2-receptor antagonists and alginates provides symptomatic relief in the majority of patients but is less effective in inducing healing of the inflamed oesophageal mucosa. Moreover recurrence of symptoms is invariable with cessation of medical therapy. Omeprazole has been shown to be a more effective treatment in a number of clinical trials[1–3]. However, there is concern in relation to the long-term effects of complete achlorhydria induced by this proton pump inhibitor. Surgical treatment is usually reserved for when there is failure of medical treatment to control symptoms, non-compliance with medication, and onset of complications. The commonest procedure performed is some form of total or incomplete fundal wrap performed through an abdominal approach. Although the results of abdominal fundoplication are good, this procedure is not without its immediate and late complications. The ligamentum teres (round ligament) sling procedure reported by Narbona-Arnau *et al.*[4] in 1965 has been well validated as an effective, low morbidity option which lengthens the abdominal segment and increases the high pressure zone at the lower oesophageal sphincter[5–7] without incurring adverse effects, such as dysphagia or the gas bloat syndrome, which may be associated with other anti-reflux procedures that involve plication of the fundus.

We have adapted this procedure for surgical laparoscopic treatment of symptomatic reflux disease unresponsive to medical treatment and report on the technique and our preliminary experience with this operation.

Patients and methods

Types and placement of trocar cannulae

Five cannulae are required (*Figure 1*): two 11·5 mm in diameter and three 5·5 mm. One of the latter is replaced by a 5·5 mm silicone cannula during the course of the operation.

The large cannulae are placed at the level of the umbilicus well laterally just beyond the linea semilunaris on either side. These are necessary for the insertion of the telescope (on either side) and the clip applicator. In addition, other operating instruments such as graspers and scissors can be introduced inside a reducing tube.

The uppermost 5·5 mm trocar cannula is placed below and to the right of the xiphoid process and is used to introduce the fan retractor that lifts the left lobe of the liver. The second 5·5 mm trocar cannula is placed to the right of the linea alba above the umbilicus. The third (left) 5·5 mm cannula is placed above (approximately 5·0 cm) and lateral to the left 11·5 mm cannula and is subsequently replaced by the silicone cannula (see below).

Special instrumentation

In addition to the standard laparoscopic equipment, the following items are essential: fan retractor (Storz, Tuttlingen, Germany), endo-ligature assembly (pusher rod, suture applicator, dry chromic catgut 1/0), pledget swab assembly, two needle holders (3 and 5 mm), clip applicator, long curved grasper and silicone cannula. The latter is essential for the introduction of the curved grasper used for the insertion of a sling around the oesophagus (*Figure 2*).

Technique of operation

The procedure consists of three sequential parts: (1) mobilization of the teres ligament with preservation of its blood supply, (2) mobilization of the abdominal oesophagus, and (3) cardiopexy with the teres ligament sling using a modification of the technique of Narbona-Arnau *et al.*[4] (*Figure 3*).

Mobilization of the ligamentum teres. An appreciation of the vascular supply and detailed anatomy of the ligamentum teres/falciform complex is essential (*Figure 4*). The blood supply comes from the liver and the peritoneal attachments. A vascular arcade (sometimes double), which is fed by hepatic branches, runs parallel to the round ligament as far as the umbilicus and must be preserved. Above the liver the two layers of peritoneum are closely apposed forming a translucent window which is outlined by a peripheral vascular suprahepatic arcade. Fine vessels traverse the window to terminate superiorly in the suprahepatic arcade and inferiorly in the serosal vasculature covering the liver. Below the liver the two peritoneal leaves are separated by a fatty layer of variable thickness which always contains large veins.

The mobilization must proceed according to a set plan to ensure preservation of the blood supply to the ligamentum teres and avoid haematoma formation. (1) Separation starts in the transparent window in the falciform ligament below the suprahepatic arcade. Electrocautery and scissors are used to divide the peritoneum along the margins of

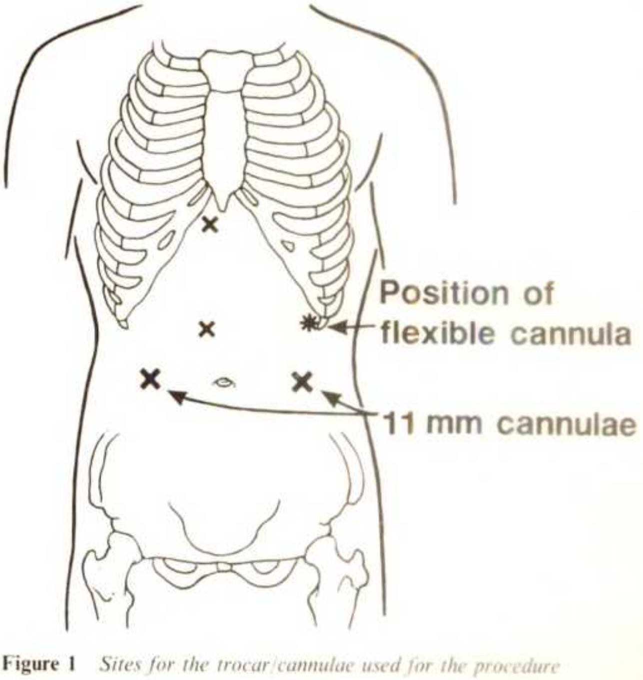

Figure 1 *Sites for the trocar/cannulae used for the procedure*

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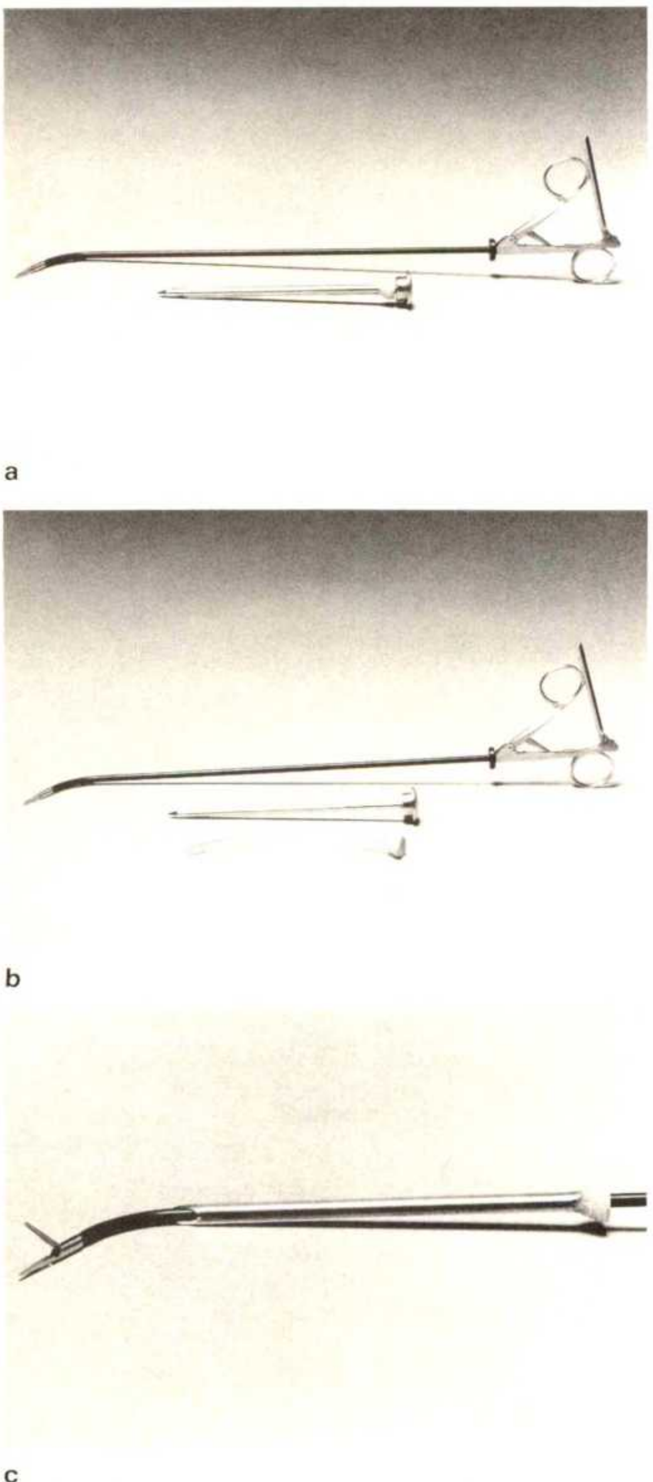

Figure 2 **a** *Long curved grasper adjacent to silicone cannula loaded with standard metal trocar.* **b** *The trocar is removed from cannula following insertion through the parieties.* **c** *Long curved atraumatic grasper inside silicone cannula*

the window leaving a 1 cm cuff on the superior surface of the liver. This separation is performed from the left side. (2) The distal limb of the arcade is next separated from surrounding fat, ligated in continuity by chromic catgut using a Roeder slip knot[8] and then divided. (3) The peritoneum on the left side of the falciform ligament is divided by electrocautery and scissors keeping well away from the vascular arcade supplying the round ligament. This process is continued up to the umbilical insertion where the end of the arcade running along the ligamentum teres is ligated in continuity with a Roeder knot using chromic catgut. (4) A second telescope connected to another light source may be inserted from the opposite side and used to transilluminate the residual fat of the falciform ligament to visualize the vessels running from the round ligament arcade to the anterior abdominal wall. These vessels are coagulated or clipped before the residual intervening fat and right peritoneal leaf is divided. We have found that this transillumination is particularly useful in avoiding bleeding and haematoma formation. It is important that the light intensity in the camera-telescope is reduced during transillumination of the falciform ligament. (5) The insertion of the ligamentum teres into the umbilicus is then cleared of surrounding tissues with cutting diathermy. It is next doubly ligated in continuity with catgut and divided. The proximal ligature is left long and used as a 'tow rope' to pull the ligament around the oesophagus at a later stage. (6) The raw area on the anterior abdominal wall and diaphragm is inspected for haemostasis and any bleeding points electrocoagulated.

Mobilization of the abdominal oesophagus. Exposure of the region is obtained by lifting the left lobe of the liver with a fan liver retractor or endoretractor which fits on the end of a 30° forward oblique telescope. The important landmark at the right lateral margin of the oesophagus is the anterior nerve of Latarjet near its origin. (1) The peritoneum is grasped to the left of the anterior nerve of Latarjet and divided with scissors medial to the nerve along the right margin of the oesophagus. It is important to keep the dissection high, near the hiatus and above the left gastric vessels. At this level only one or two small veins cross the oesophagus. These are electrocoagulated and divided by scissors. (2) Dissection of the right margin of the abdominal oesophagus proceeds with pledget and sucker dissection to expose the right lateral wall of the gullet. The posterior vagus is encountered at this stage and dissection is continued medial to this nerve until the posterior wall of the oesophagus is reached. The plane is opened and extended in a proximal direction towards the mediastinum. The dissection should not be carried downwards as this will rupture branches of the left gastric artery and cause bleeding. (3) The direction of the telescope is then adjusted to expose the oesophagogastric junction on the left side and the gastrophrenic peritoneal reflection is divided. A few phrenic vessels passing to the fundus require electrocoagulation before division. Thereafter, the left margin of the oesophagus is mobilized using blunt dissection with a pledget swab and continued until the posterior wall of the oesophagus is reached. One or two phrenic vessels posterolateral to the gullet are often encountered and can cause bleeding, but haemostasis can be achieved by grasping the bleeding point before electrocautery. (4) The peritoneum over the anterior wall of the oesophagus is then divided and blunt dissection by pledget swab in an upward direction is used to tease the peritoneal lining and the phreno-oesophageal membrane from the anterior wall of the oesophagus. A few vessels on the left side of the oesophagogastric junction in the region of the nerves of Grassi require electrocoagulation before they are divided by scissors. (5) A curved long grasper introduced

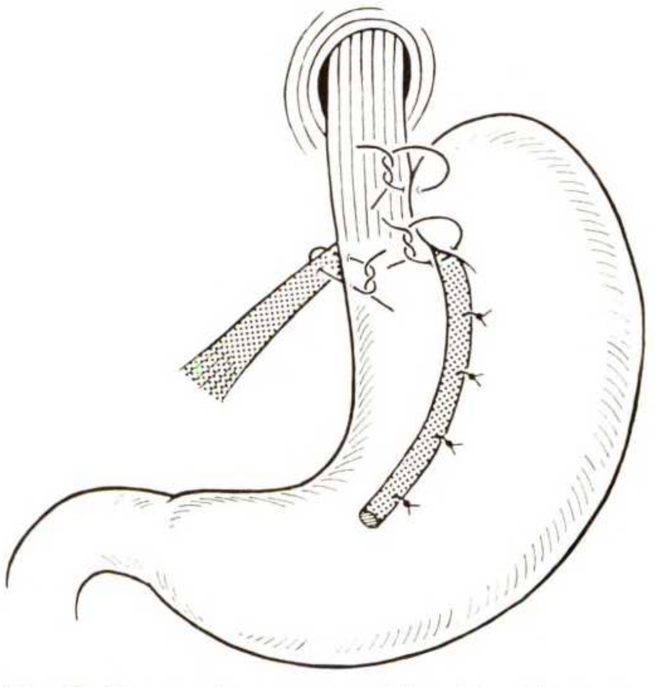

Figure 3 *Diagrammatic representation of the technique of ligamentum teres cardiopexy of Narbona-Arnau* et al.

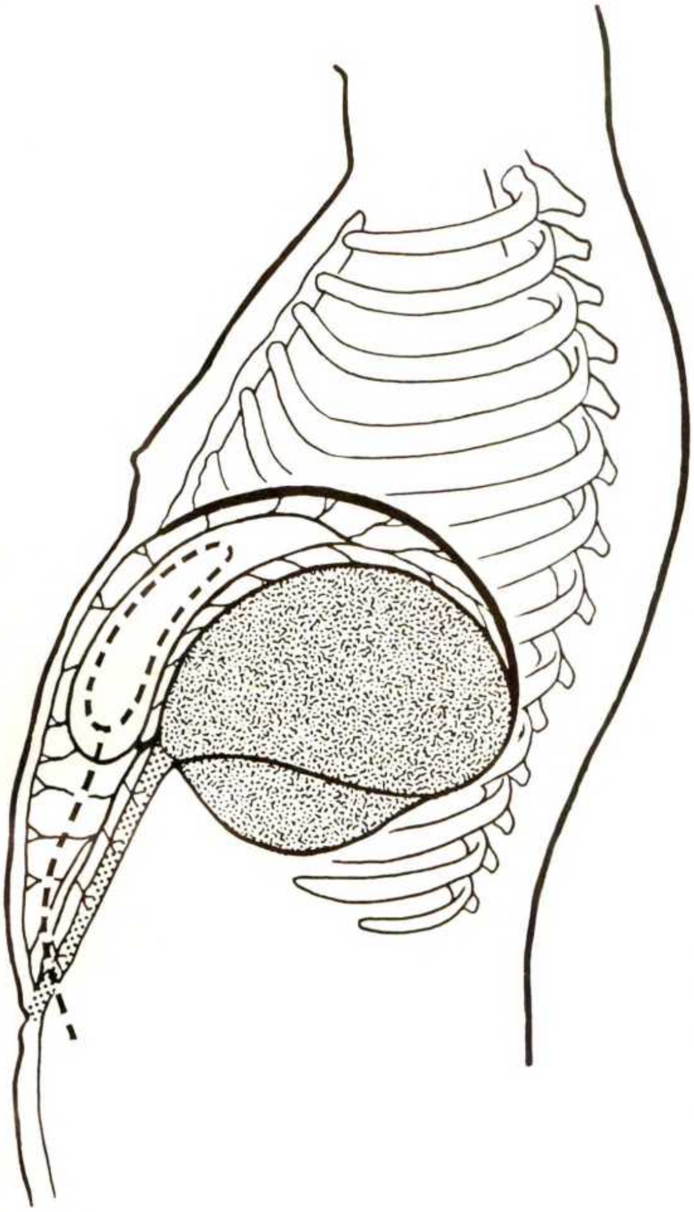

Figure 4 *Vascular anatomy of the ligamentum teres/falciform ligament complex. During the mobilization of the round ligament, the vascular arcade alongside it derived from the hepatic vessels must be kept intact. The dotted line represents the line of division of the suprahepatic window and the line of separation of the falciform fat from the teres ligament*

through the abdominal wall inside a flexible silicone cannula (replacing the left 5·5 mm hypochondrial cannula) is then inserted with its jaws closed. The grasper is introduced along the posterior wall of the oesophagus from the right side and made to emerge to the left of the oesophagogastric junction. Its jaws are then opened to grasp a vascular silicone sling. The latter is introduced by a straight grasper through a small stab wound high in the left hypochondrium. The sling is pulled around the gullet by careful withdrawal of the curved grasper and following transfer to the straight grasper, is exteriorized. Traction is then applied externally to the two ends of the sling which are secured at skin level by an artery forceps. The traction caused by the sling lifts the abdominal oesophagus forwards away from the crura and the hiatus and allows completion of the posterior mobilization by pledget dissection (*Figure 5*). (6) The curved grasper is inserted behind the oesophagus from the left side and used to pick up the ligature on the ligamentum teres (tow rope) thereby guiding the ligament around the back of the oesophagus and left side of the oesophagogastric junction. Continued traction brings the ligamentum teres along the anterior wall of the stomach parallel to the lesser curve.

Manometrically controlled cardiopexy. (1) The end of the ligament is then grasped and pulled down along the line of the oblique fibres of the stomach. The degree of traction influences both the length of the intra-abdominal segment and the pressure within the lower oesophageal sphincter. The degree of traction is adjusted by oesophageal manometry with zero calibration corresponding to the gastric pressure. The traction on the ligamentum teres is adjusted to achieve a pressure increment of 15–20 mmHg. This traction is then maintained unchanged throughout the rest of the procedure. Suturing is performed using 3/0 black silk sutures using the two-needle holder technique with internal knotting. (2) The first suture anchors the ligamentum teres to the oesophagogastric junction on the left side and is of the mattress type. When tied, this suture fixes the apex of the sling in the intended position (*Figure 6a*). (3) The fundus of the stomach above the accentuated gastro-oesophageal angle (of His) is sutured to the adjacent oesophagus above the apex of the sling (*Figure 6b*). (4) Four sutures are then used to fix the rest of the ligamentum teres to the anterior wall of the stomach along the line of the oblique fibre (roughly parallel to the lesser curve) over a distance of 5–6 cm (*Figure 6c*). The endoscopic appearance at the end of the operation is shown in *Figure 7*.

Results

The procedure has been performed in five patients, two of whom had a reducible hiatus hernia. The postoperative period was uneventful. Fluids and soft feeds were started on the following day. The patients (three women and two men, aged 30–41 years) were all discharged by the fifth postoperative day. Ileus was not observed in any of the patients despite long operative times (2·5–5 h). Mobilization of the round ligament and the oesophagus can now be completed within 1·5–2 h in the absence of a hiatus hernia. However, oesophageal dissection is difficult and prolonged in the presence of a hiatus hernia owing to the oesophageal shortening and the presence of a fat pad associated with the hernial sac. In these cases, dissection has to be advanced to the lower mediastinum to achieve adequate lengthening of the lower oesophagus.

To date all patients have been relieved of their reflux symptoms and have not complained of any dysphagia or gas bloat symptoms. However, the follow-up is short (1–6 months) and no realistic adjudication is possible. Oesophageal manometry, endoscopy, 24-h pH monitoring, isotope transit (^{99m}Tc-labelled solid egg bolus) and barium contrast studies have so far been repeated in three patients at 1–2 months after the procedure. The postoperative appearances on contrast radiology are distinctive. There is lengthening of the intra-abdominal segment of the oesophagus owing to the depression of the gastro-oesophageal junction equivalent to the length of two vertebral bodies (6 cm) and a marked accentuation of the angle of His. The 24-h ambulatory pH has shown a normal pattern of lower oesophageal pH in both the erect and supine positions and oesophageal transit using the labelled egg white bolus technique has been within the normal of 12 s. The details of the postoperative objective changes relevant

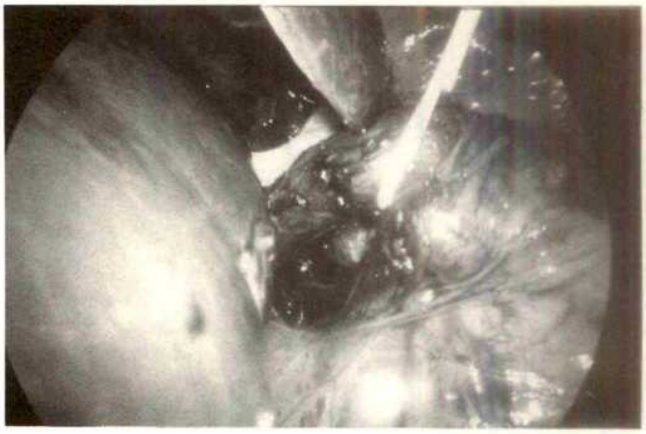

Figure 5 *Endoscopic photograph of the silicone vascular sling around the oesophagus. Traction on the sling lifts the oesophagus off the crura and hiatus enabling completion of the posterior mobilization by pledget dissection*

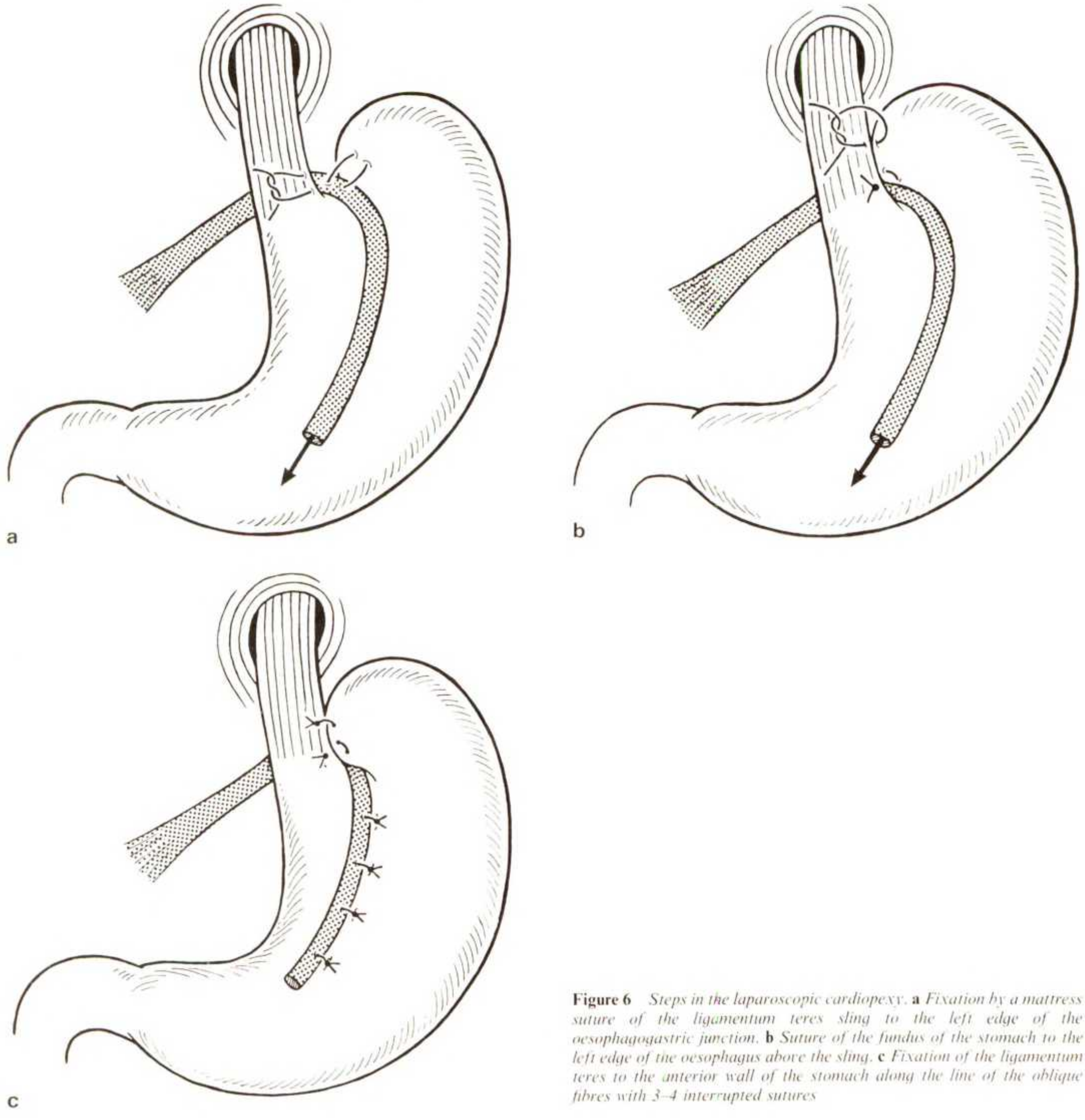

Figure 6 *Steps in the laparoscopic cardiopexy.* **a** *Fixation by a mattress suture of the ligamentum teres sling to the left edge of the oesophagogastric junction.* **b** *Suture of the fundus of the stomach to the left edge of the oesophagus above the sling.* **c** *Fixation of the ligamentum teres to the anterior wall of the stomach along the line of the oblique fibres with 3–4 interrupted sutures*

Figure 7 *Endoscopic photograph of the completed operation*

to the pathophysiology of the disease will be reported after more extensive experience with the procedure.

Discussion

The essential feature of the cardiopexy of Narbona-Arnau consists of suture fixation of the round ligament sling to the oesophagogastric junction and anterior wall of the stomach[4]. In the operation reported by Rampal *et al.* in 1964 the end of the ligamentum teres sling is attached to itself[9]. This antireflux procedure, which is similar in concept to the modern Angelchick prosthesis, has certain potential disadvantages. Perhaps the most important of these concerns the real risk of the oesophagogastric junction slipping through the sling. There are no large reported series of the Rampal cardiopexy.

The laparoscopic procedure described in this report reproduces the steps of the ligamentum teres cardiopexy of Narbona-Arnau *et al.*[4] except for the omission of the anchoring suture on the right side of the oesophagogastric junction. We omitted this suture to minimize the risk of devascularization of the round ligament and to obtain the maximum downward displacement of the oesophagogastric junction by the sling. The resulting increased length of the intra-abdominal segment constitutes the most important aspect of the antireflux mechanism created in this procedure. In accordance with the La Place law, the extended abdominal oesophageal segment is then able to function as a flutter valve with apposition of the anterior and posterior walls whenever the intra-abdominal pressure rises[10].

The operation has been made feasible by the design and use of the curved grasper which is introduced into the peritoneal cavity through a flexible silicone cannula. Retraction of the left lobe of the liver by the fan retractor and or the endoretractor facilitates exposure of the cardio-oesophageal junction.

Laparoscopic suturing and internal knotting with the present generation of needle holders and sutures is difficult and slow. Better instrument design, which will avoid the problems of needle swivel and facilitate internal knotting, is currently being addressed. These developments should reduce significantly the operating time in procedures requiring laparoscopic suturing.

It is not possible to draw any conclusions regarding the long-term benefit of this laparoscopic approach. However, the equivalent open operation in a large reported series rendered 75 per cent of patients asymptomatic[5-7].

Acknowledgements

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Gastrointestinal mucormycosis

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Twenty patients with gastrointestinal mucormycosis are reviewed. This often fatal opportunistic fungal infection was diagnosed histologically, and was categorized as colonization (five patients), infiltration (seven patients), or vascular invasion (eight patients). There were no fatalities from colonization. In 10 patients, mucormycosis complicated peptic ulcer disease. Seven of these patients had infiltrative or invasive disease. The presentation and operative findings mimicked malignancy in five of these seven patients, and six had successful surgical intervention. The other patient was cured by medical therapy alone. Ten patients had infection associated with other gastrointestinal diseases: post-traumatic peritonitis (four patients), transmural amoebiasis (two patients), tuberculosis (one patient), gastroenteritis (one patient), gastric carcinoma (one patient) and diabetes (one patient). Eight patients had significant infection and only one survived. In this series, mucormycosis had a less aggressive course when complicating peptic ulcer than when it occurred in association with other gut diseases.

Mucormycosis is an uncommon, frequently fatal, opportunistic fungal infection[1]. Rhinocerebral and pulmonary disease are the most common forms and usually occur in immunocompromised patients[2]. Gastrointestinal infection is rare, the stomach being the most frequently involved site[2–4]. Colonization of benign peptic ulcers is described, but does not influence the natural history of the disease. However, where true vascular invasion with this fungus is present histologically, irrespective of the gut site, the outcome is usually fatal[4,5].

Our experience with this disease has led us to believe that there is a spectrum of severity and that survival may occur even with advanced disease. We therefore undertook to analyse the clinical features and review the histological sections from patients with gastrointestinal mucormycosis.

Patients and methods

The case records of all patients who had histologically confirmed mucormycosis of the gastrointestinal tract diagnosed during life over a 5-year period (1984–1988) were identified by a computer-aided search using diagnostic and pathological index codes. The case records were scrutinized and the following data extracted: demographic characteristics, presentation, treatment, outcome and histological assessment.

The histological sections were reviewed and the disease categorized as colonization, infiltration or vascular invasion. Colonization was diagnosed when the fungus was seen in ulcer exudate, necrotic tissue or mucosa. Infiltration was the term applied when the fungus was present within deeper viable tissue. Vascular invasive disease represented vessel invasion by mucormycosis. Examples of these three categories are illustrated in *Figures 1, 2* and *3*. The characteristic macroscopic features of the vascular invasive form are diffuse necrotic lesions with black discoloration.

Results

In 10 patients, mucormycosis complicated peptic ulcer disease; four had associated additional debility from malnutrition and alcoholism. The remaining 10 patients had mucormycosis complicating other gastrointestinal disease as shown in *Table 1*.

Colonization with mucormycosis occurred in five patients. Three had intractable peptic ulcer disease which required surgery. Colonization also occurred in one patient with an ulcerated gastric carcinoma and one patient with rectal tuberculosis. Treatment in this group was that of the underlying disease and it was not associated with fatality. None of these patients received anti-fungal treatment.

Infiltrative and vascular invasive mucormycosis developed as complications in seven patients with peptic ulceration and eight patients with other diseases. Of the seven patients with peptic ulcer disease, all presented with a complication of perforation, bleeding or obstruction. The presentation mimicked malignancy in five patients, all of whom had giant ulcers. In three patients, preoperative endoscopy and barium

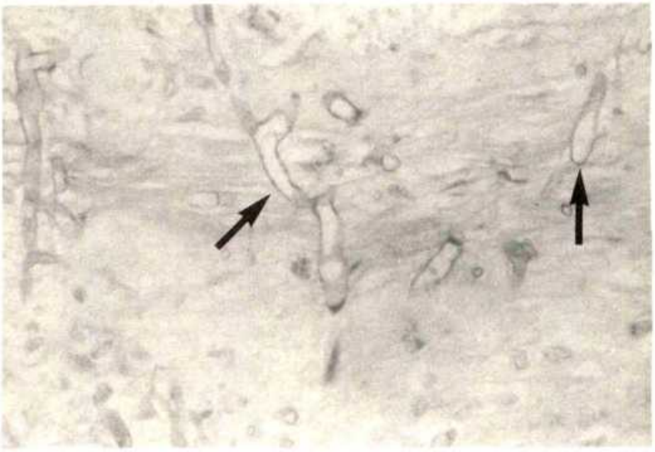

Figure 1 *Colonization: several hyphae arrowed in necrotic tissue. (PAS preparations × 400)*

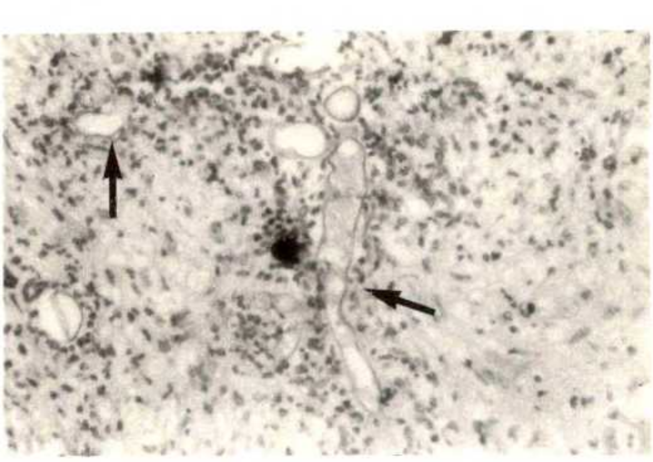

Figure 2 *Infiltration: fungal hyphae arrowed in viable tissue but not invading vascular structures. (PAS preparations × 400)*

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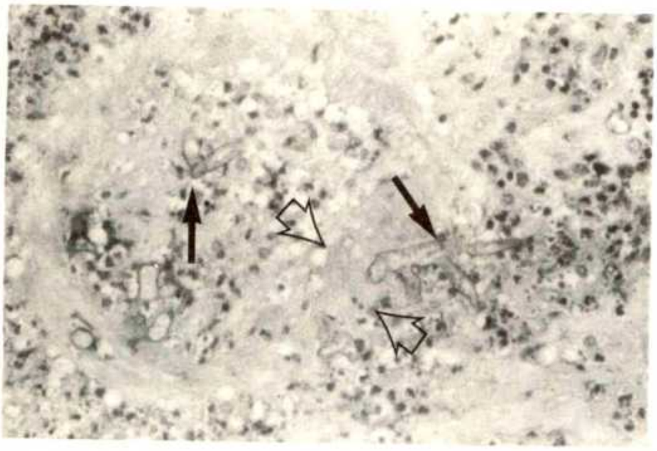

Figure 3 *Invasion: vessel wall indicated by open arrows. Fungal hyphae arrowed in vessel wall (right) and lumen (left). PAS preparations × 400)*

Table 1 *Diseases complicated by mucormycosis according to histological category*

Associated disease	Histological category		
	Colonization	Infiltration	Invasion
Peptic ulceration	3	5	2
Gastric carcinoma	1	0	0
Post-traumatic peritonitis	0	1	3
Transmural amoebiasis	0	1	1
Gastroenteritis	0	0	1
Rectal tuberculosis	1	0	0
Diabetes mellitus	0	0	1
Total	5	7	8

meal suggested a diagnosis of malignancy, but endoscopic biopsy revealed mucormycosis. Similarly, the operative appearance in four cases suggested malignancy with hard mass lesions penetrating adjacent tissues and diffuse necrotic ulcers with rolled edges. All but one patient required surgery for their complicated ulcer *per se*, and two patients posed technical operative problems because of gross destruction of the duodenum and surrounding structures.

The patient treated non-operatively presented with gastric outlet obstruction and demonstrated a large destructive duodenal lesion which appeared malignant. However, biopsies showed infiltrative mucormycosis without evidence of malignancy. The patient was treated conservatively and received amphotericin-B and sucralfate. At endoscopy 2 months later, the lesion had healed with a scarred but patent duodenum. Three other patients received parenteral amphotericin-B, but only after the diagnosis was made from operative specimens. All seven patients in this group with significant mucormycosis complicating peptic ulcers made a full recovery.

Of the eight patients with infiltrative and vascular invasive mucormycosis complicating other diseases, one was a diabetic. This patient had progressive mucormycotic oesophageal ulceration and, despite intravenous amphotericin-B and supportive treatment, died of progressive disease.

Table 2 *Mortality from gastrointestinal mucormycosis*

	Survival	Death
Colonization	5	0
Infiltration		
Peptic ulcer	5	0
Amoebic colitis	1	0
Post-traumatic peritonitis	0	1
Vascular invasion		
Peptic ulcer	2	0
Gastroenteritis	0	1
Post-traumatic peritonitis	0	3
Diabetes	0	1
Amoebic colitis	0	1

The remaining seven patients developed mucormycosis with a background of anaerobic bacterial peritonitis because of an identifiable cause, as shown in *Table 1*. Four patients were trauma victims. They were previously healthy individuals who had delayed operative treatment of established peritonitis caused by bowel perforations. In two cases, the underlying disease was transmural amoebiasis and in another it was gastroenteritis septicaemia. The operative findings in the group as a whole were those of progressive bowel necrosis, and four developed mucormycotic abdominal wall necrosis. Only three of the seven patients received amphotericin-B, owing to delayed diagnosis. Despite resectional bowel surgery, repeated laparotomies and supportive measures, they all died except one patient with underlying amoebic colitis.

Mortality from gastrointestinal mucormycosis is shown in *Table 2*. All patients with colonization survived. Six of the seven patients with infiltrative disease and only two of the eight patients with invasive disease survived. There were no deaths when mucormycosis complicated peptic ulceration, despite two of these patients having the vascular invasive form of the disease.

Discussion

Fungi of the order *Mucorales* have minimal intrinsic pathogenicity but can cause aggressive and fulminant infections, particularly in immunocompromised and diabetic patients. Mucormycosis has been described in most sites of the body[6]. The gastrointestinal variants of the disease are uncommon and most of the previous reports of this condition have come from Southern Africa[4,7–10], but it has been reported sporadically in America and Europe[5,11,12]. In all our patients, mucormycosis complicated an underlying disease. In most patients this was a local disease process, usually peptic ulceration. Only one patient, with diabetes, had a purely systemic disease. This concurs with other reviews in which local abnormalities of the gastrointestinal tract predominate in predisposing to mucormycosis of the gut[2,9]. We feel that the development of persistent peritonitis from any cause is a significant predisposing factor for secondary mucormycosis infection which has not previously been emphasized. The four previously well patients with post-traumatic peritonitis and subsequent mucor infection illustrate this point.

Lawson and Schmaman[4] have polarized the disease in the stomach and duodenum histologically into colonization and vascular invasive forms. We would agree that colonization is of little clinical significance, but we propose a broader spectrum of the disease than that to which they have alluded. In our opinion, an additional category of infiltrative disease exists where the fungus invades healthy tissue adjacent to ulceration, and, though carrying less risk of mortality than the invasive form, still represents severe clinical disease. Macroscopic features may enable clinical diagnosis to be made at operation, but all too often we had problems with the intraoperative recognition of the disease.

The data from this series confirm that it is giant peptic ulcer that predisposes to mucormycosis and this combination mimics malignancy. In the past, the diagnosis of gastroduodenal mucormycosis was made at autopsy or from resected specimens of patients who eventually died from their disease[4,7–10]. Endoscopic biopsy before any surgical intervention identifies the presence of the fungus. Small biopsies may not allow accurate histological staging of the disease. Hence, the interpretation of the aggressiveness of the disease must be made on clinical grounds. If the patient is well and a clinically benign ulcer is seen at endoscopy, specific ulcer treatment and close surveillance of the healing process is all that is indicated. If there is obvious malnutrition and anaemia, and a cancer-like ulcer is seen on endoscopy, anti-fungal and specific ulcer therapy may give a satisfactory result, as happened in one of our patients. However, if there is deterioration in spite of this treatment or an added complication supervenes, surgery is indicated. In our hands, individually tailored surgery has been universally successful and Schulman *et al.*[13] have also reported an isolated survivor from invasive disease; earlier reports[4,7] of invasive mucormycosis held that the course was invariably fatal. We feel that it is the absence of generalized peritonitis in our peptic ulceration patients which explains their improved prognosis when compared with other studies or involvement at other gut sites. When mucormycosis complicates generalized peritonitis, we believe that an aggressive resectional surgical approach with planned relaparotomy is the only policy which will produce the occasional survivor.

It is far from clear what effect anti-fungal treatment has on the outcome in severe gastrointestinal mucormycosis because invariably it is only instituted several days following surgical intervention when histological confirmation of the diagnosis is obtained. It seems logical to use amphotericin-B systemically as it has proven efficacy in rhinocerebral infection[14,2]. One should continue therapy for as long as there is clinical evidence of infection.

In conclusion, we believe that there is a clinical and histological spectrum of severity of mucormycosis, and that an infiltrative histological category exists which represents severe clinical disease. In this series, severe clinical mucormycosis was most commonly seen in association with giant peptic ulcers. Survival occurred where the disease was not associated with generalized peritonitis.

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Chemotherapy and surgery for locally advanced cancer of the cardia and fundus: phase II study with methotrexate and 5-fluorouracil

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Locally advanced cancer of the cardia and fundus might be cured by surgical resection. Poor results after surgery in stage IIIB and stage IV disease prompted a study of neoadjuvant chemotherapy. Treatment included four cycles of high doses of methotrexate (1·5 g/m²) and high doses of 5-fluorouracil (1·5 g/m²) followed by surgery in those patients with lesions then found to be resectable. Twenty patients with tumours staged as IIIB or IV were entered; 17 patients completed the four courses of chemotherapy and 14 underwent re-exploration. Eight patients achieved tumour reduction enabling resection. Five patients underwent total gastrectomy with distal pancreatectomy and splenectomy en bloc *and three patients had an oesophagogastrectomy. There were no treatment-related deaths and toxicity was tolerable. Two patients were alive 54 and 41 months after chemotherapy with no evidence of disease. Locoregional recurrence developed in five patients and metastatic disease in one. Their median survival was 22 months.*

Adenocarcinomas of the cardia and the proximal third of the stomach can be grouped together because they have a comparable pattern of lymphatic spread and local invasion, and the methods of treatment are similar[1,2]. *En bloc* excision of the tumour with the potentially invaded nodes may offer the patient cure if distant metastases remain absent.

Promising results from major resections combined with extended lymph node dissection are reported in the Japanese literature[3–6], and even in stage III or IV disease 5-year survival rates of 27 and 20 per cent respectively have been achieved[3].

In the Western hemisphere, however, the results are rather poor. Calan *et al.*[7] obtained a 5-year survival rate of 12 per cent in stage III disease but those with stage IV disease died within 1 year after resection[1]. Others report no survivors beyond the fourth year if they presented with stage III and IV disease[8].

Gastric cancer is partially responsive to cytotoxic chemotherapy and combination regimens may allow complete responses (a recent EORTC study showed 13 per cent of 67 patients to have complete responses)[9]. Such a regimen may eradicate microscopic disease left after curative surgery for gastric cancer and might make unresectable tumours amenable to palliative surgery. The EORTC regimen consisted of methotrexate and 5-fluorouracil, a combination producing only short-term toxicity. This has been used in a neoadjuvant setting in patients with unresectable cancer.

Patients and methods

Patients studied

Twenty consecutive patients (18 men) with locally advanced cancer of the cardia and fundus, considered incurable by conventional surgical treatment, were entered The average age was 53 years (range 36–68 years). In 12 patients the tumour was located in the cardia and in eight in the fundus. Patients were entered between March 1985 and June 1988. Criteria for entry into the study included histologically proven adenocarcinoma of the cardia and gastric fundus, age below 70 years, absence of previous or concomitant malignancies, no previous chemotherapy or radiotherapy and normal renal and liver function.

Assessment of resectability

Preoperative computed tomographic (CT) scanning was carried out in all patients from the tracheal bifurcation to the lower border of the pancreas. Three patients were considered incurable because of massive invasion of adjacent structures and involved distant, abdominal lymph nodes more than 3 cm away from the primary tumour (N_2–N_3TNM)

In 17 patients, staging based on CT scanning and laparotomy showed that macroscopic disease could not be successfully removed At laparotomy, the extent of tumour invasion, the level of lymph node involvement and the presence of peritoneal or liver metastases were assessed or confirmed by frozen section examination Findings precluding cure by primary surgery were massive invasion of the retroperitoneum, fixation to the aorta and metastatic nodes at the origin of the left gastric artery, coeliac axis or the upper border of the pancreas. The degree of tumour differentiation is summarized in *Table 1*, as is the prechemotherapeutic stage according to the tumour, node, metastasis (TNM) staging system. There were 18 T_4 and two T_3 tumours. Nodal involvement (N_2) could be assessed in 18 patients All

Table 1 *Characteristics of the 20 patients included in the study*

Average age (range), years	53 (36–68)
Sex (M∶F)	18∶2
Tumour location	
Cardia	12
Fundus	8
Histological grade of adenocarcinoma	
Well differentiated	2
Moderately differentiated	8
Poorly differentiated	10
Tumour stage*	
IIIB	2
III/IV	2
IV	16

* Stage assessed using the tumour, node, metastasis classification[10]

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patients had stage IIIB or stage IV disease according to the new Union International Contra le Cancrum (UICC) classification[10].

Chemotherapy

Chemotherapy consisted of 1·5 g/m^2 methotrexate followed 1 h later by 1 5 g/m^2 5-fluorouracil, both drugs being administered in a 30-min intravenous infusion Leucovorin rescue consisted of 15 mg/m^2 orally every 6 h starting after 24 h for a total of 48 h. Sodium bicarbonate, 1 4 per cent (2 litres), was given on the day of chemotherapy to keep the urine pH above 7·0. Four courses were given in a 4-week cycle

Unless progression was obvious (re)laparotomy was performed 4 weeks after the last course

Surgery

Surgery was performed with the same surgical team (R V. and J T P.) attempting to resect the primary tumour with the involved groups of regional lymph nodes when feasible All macroscopically malignant disease was removed by *en bloc* resection, taking out adjacent organs such as spleen, distal pancreas, lower oesophagus, transverse colon and coeliac lymph adenectomy whenever necessary.

Results

Table 2 shows the outcome in the 20 patients. Chemotherapy was discontinued in three patients. One patient had a fatal gastric haemorrhage from the primary tumour, one proved to have hepatic metastases and progression of the primary tumour, and the third patient withdrew after two courses. Toxicity was moderate, well tolerated and primarily limited to mild mucositis in all patients. In all, 17 patients finished the four courses of chemotherapy. Postchemotherapeutic CT scan or clinical evaluation showed no tumour progression in two patients. The other patients had stable disease on admission for a second attempt at resection. In one patient dementia progressed during chemotherapy and surgery was cancelled.

Fourteen patients underwent a second laparotomy to attempt tumour resection. Presence of liver metastases, peritoneal seedings and remote nodal metastases in the para-aortic or hepatic hilar areas were excluded. In six patients (cases 7–12, *Table 2*), staging by laparotomy and thoracotomy in three patients disclosed stable disease or tumour progression and resection was not considered justified.

Downstaging was evident on laparotomy in six patients (cases 13–17 and 20). Tumour-free resection margins were obtained in these patients and in two other patients (cases 18 and 19) with regression insufficient for downstaging. In five patients (cases 14, 15, 18–20) total gastrectomy was performed *en bloc* with omentectomy, splenectomy and distal pancreatectomy (one laparotomy and four thoracolaparotomies).

Reconstruction was achieved by a retrocolic Roux loop anastomosed end-to-end to the oesophagus. Three patients (cases 13, 16 and 17) underwent a resection of the proximal stomach and lower oesophagus with reconstruction by means of a gastric tube. Dehiscence of an oesophagojejunal anastomosis occurred in one patient and prolonged the hospital stay to 52 days. Another patient developed a chyloperitoneum which resolved spontaneously during a hospital stay of 48 days. The postoperative course of the other patients was uneventful and the average postoperative hospital stay was 17 days (range 11–36 days).

Patients who did not finish chemotherapy (three cases) or in whom no second laparotomy was carried out (three cases) died at a mean of 5 months after first chemotherapy (range 1–9 months).

Six patients with a remaining unresectable tumour at the second laparotomy survived on average 12 months after the first chemotherapy course (range 6–24 months). Among the eight patients who underwent a resection, two are alive with no evidence of disease 54 and 41 months after the first course of chemotherapy.

Six patients developed recurrent disease and died at a median of 22 months after the first chemotherapy course (range 14–36 months). In five of these patients the first manifestation of tumour recurrence was locoregional.

Discussion

Adenocarcinoma of the cardia is a tumour of the gastro-oesophageal junction within 5 cm of the margin of the mucosa, the so-called Z-line[11]. Nishi *et al.*[12] defined the gastric cardia as the area up to 2 cm on both sides of the Z-line. Approximately 40–50 per cent of patients are considered incurable by surgical resection at the time of diagnosis[13,14]. Results after adequate surgery are determined by the extent of the disease and show a wide variation. For all patients undergoing resection the 5-year survival rate ranges from 4 5 to 20 per cent[15]. A similar variation can be found in data for the 30-day mortality rate after surgery. Comparing data from different centres is difficult because there are no standard criteria for resectability, palliation and cure. The classification for gastric cancer was used as being the most appropriate but this TNM classification has shortcomings[10]: lack of consideration of the tumour size, extranodal disease, lymphatic and vascular invasion. The Japanese added the N_3 and N_4 status for invasion of nodes beyond the scope of the *en bloc* resection, precluding any comparison with other data[3–6].

The patients in this study all had a poor prognosis. In 17 patients elaborate staging was carried out by computed tomography and laparotomy. Although CT scanning does not have the accuracy to allow its routine use for staging, this investigation was used in all patients. Computed tomography underestimates the extent of these tumours[16–18], but the findings in three patients were convincing enough to preclude an attempt at primary resection. All patients had at least stage IIIB disease. Fourteen patients underwent a second laparotomy; in eight, definite regression of tumour was found and resection was possible. As a result of fibrosis imitating residual tumour, resectability is not evaluable by CT scanning as no response was detectable in any of the patients who were found to have resectable disease at second laparotomy. The fatal outcome of most of these patients seems to be in conflict with the promising pathological downstaging. One of the two long-term survivors had no downstaging after the four courses of chemotherapy.

Stage III and IV cancers of the gastric cardia are a challenge for any oncologist, and Papachristou and Fortner[8] consider these tumours incurable by surgical means regardless of the type of resection used. Adjuvant chemotherapy following resection for cure is not recommended for routine use in patients with gastric cancer[18]. Preoperative chemotherapy described here is feasible and well tolerated, and may have some beneficial effect in individual cases with initially unresectable adenocarcinoma of gastric cardia or fundus Resectability of 40 per cent with a median survival of 22 months in this group was found.

A similar but multicentre study carried out by a German group has recently been published. The neoadjuvant chemotherapy consisted of etoposide, doxorubicin and cisplatin. Their results, with 23 per cent long-term survivors (8 of 34 with 14 months' median follow-up), seem to be somewhat better, either because of patient selection and different sites of the primary tumours, or the different drug combination[19]. It remains unclear whether the preoperative treatment influenced the outcome of the disease. The 10 per cent long-term survival rate in this group seems to be higher than would be expected for patients with this stage of disease[8,15].

Further studies should be directed at a more effective chemotherapy regimen; at better selection of patients, such as identification of distant metastases by sampling para-aortic (N_4) nodes; and at more adequate prevention of local recurrence, for instance with intraoperative radiotherapy or intraperitoneal chemotherapy[20]. Finally, the ultimate value will have to be defined in a controlled study.

Table 2 *Clinicopathological findings of the 20 patients included in the study*

Case	Age (years)	Sex	Location	Histological type of adenocarcinoma	Prechemotherapy staging (first laparotomy and/or CT)	Postchemotherapy staging (second laparotomy)	Total courses of chemotherapy	Response (CT or clinical)	Recurrences	Survival (months)
Remains incurable, no 'second look' laparotomy										
1	41	M	Cardia	Poorly differentiated	$T_4N_2M_0$	—	3	Progressive disease	—	5
2	56	M	Fundus	Moderately differentiated	$T_4N_2M_0$	—	2	—*	—	5
3	61	M	Cardia	Moderately differentiated	$T_3N_2M_0$	—	4	Stable disease†	—	9
4	60	M	Cardia	Moderately differentiated	$T_4N_2M_0$	—	1	—‡	—	1
5	66	M	Cardia	Poorly differentiated	$T_4N_2M_0$	—	4	Progressive disease	—	5
6	42	M	Fundus	Poorly differentiated	$T_4N_2M_0$	—	4	Progressive disease	—	8
Still incurable at relaparotomy										
7	42	F	Cardia	Well differentiated	$cT_4N_2M_0$	$T_4N_2M_0$	4	Stable disease§	—	24
8	36	M	Cardia	Poorly differentiated	$T_3N_2M_0$	$T_4N_3M_0$	4	Stable disease	—	9
9	40	M	Cardia	Poorly differentiated	$T_4N_2M_0$	$T_3N_2M_0$	4	Stable disease	—	8
10	58	M	Cardia	Moderately differentiated	$cT_4N_2M_0$	$T_3N_2M_1$	4	Stable disease	—	6
11	56	M	Fundus	Poorly differentiated	$T_4N_2M_0$	$T_4N_2M_1$	4	Stable disease	—	6
12	51	M	Cardia	Moderately differentiated	$T_4N_2M_0$	$T_3N_2M_0$	4	Stable disease	—	17
Potentially curative resections										
13	65	M	Cardia	Moderately differentiated	$T_4N_xM_0$	$T_3N_0M_0$	4	Stable disease	Peritoneal carcinoma	36
14	47	M	Fundus	Poorly differentiated	$T_4N_xM_0$	$T_3N_0M_0$	4	Stable disease	Locoregional disease/ peritoneal carcinoma	20
15	54	M	Fundus	Moderately differentiated	$T_4N_2M_0$	$T_3N_1M_0$	4	Stable disease	Locoregional disease	27
16	57	M	Cardia	Well differentiated	$cT_4N_2M_0$	$T_3N_0M_0$	4	Stable disease	Locoregional disease/ distant metastases	16
17	61	M	Cardia	Poorly differentiated	$T_4N_2M_0$	$T_3N_2M_0$	4	Stable disease	Locoregional disease/ distant metastases	14
18	68	M	Fundus	Moderately differentiated	$T_4N_2M_0$	$T_4N_2M_0$	4	Stable disease	Locoregional disease/ distant metastases	18
19	47	F	Fundus	Poorly differentiated	$T_4N_2M_0$	$T_4N_2M_0$	4	Stable disease	No evidence of disease	41
20	63	M	Fundus	Poorly differentiated	$T_4N_2M_0$	$T_3N_1M_0$	4	Stable disease	No evidence of disease	54

CT, Computed tomography; TNM, tumour, node, metastasis. * Withdrew; † progressive mental disorder, ‡ fatal gastric haemorrhage, § stable disease for several months on six courses of epiadriamycin 6 mg/m^2 per 24 h (second line treatment)

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Percutaneous flexible choledochoscopy: a simple method for retained common bile duct stone removal

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Conventional methods of treatment of retained common bile duct stones found on T tube cholangiography after common bile duct exploration include percutaneous extraction under fluoroscopic control and endoscopic sphincterotomy. Four cases of percutaneous stone extraction under direct vision using the flexible choledochoscope are described. Clearance of the bile ducts was achieved at one sitting in three cases and four sittings in one case. Follow-up tube cholangiography was performed in two cases and confirmed complete clearance. Percutaneous endoscopic stone extraction can be performed by any surgeon with experience of flexible choledochoscopy and offers the advantages of a minimally invasive procedure without the use of specialized equipment.

The treatment of retained common bile duct stones usually requires expertise outside the field of most general surgeons and includes percutaneous extraction with a steerable wire basket under fluoroscopic imaging (Burhenne technique)[1] or endoscopic sphincterotomy with stone extraction[2]. Both methods not only require the skills of other hospital departments but also the use of additional equipment, neither of which may be immediately available to the surgeon.

We report the use of the flexible choledochoscope for percutaneous removal of retained common bile duct stones under direct vision via the T tube tract.

Patients and methods

Six patients were referred with retained common bile duct stones found on T tube cholangiography after cholecystectomy and exploration of the common bile duct The patients were aged between 21 and 84 years The T tube was left *in situ* for a minimum of 6 weeks to enable the formation of a fibrous tract. Provided there was free flow into the duodenum the T tube was spigotted and coiled up under a dressing to minimize inconvenience to the patient. A T tube cholangiogram taken at 6 weeks was used to confirm the continued presence of common bile duct stones In two patients the stones were found to have passed spontaneously. The remaining four patients underwent percutaneous extraction of the retained stones via the T tube tract using a flexible choledochoscope

Intravenous sedation with a benzodiazepine was used and prophylactic antibiotics administered. On removal of the T tube the flexible choledochoscope (CHF-P 10, Olympus, Southend, UK) was inserted into the tract with continuous saline irrigation and then manoeuvred into the common bile duct under direct vision Examination of the proximal bile ducts was performed before distal instrumentation. Retained stones were extracted using a Dormia basket or removed by crushing and flushing into the duodenum under direct vision. At the end of the procedure a 16 Ch latex Foley catheter was inserted down the tract to allow subsequent tube cholangiography

On confirmation of bile duct clearance by tube cholangiography the Foley catheter was removed.

Results

The choledochoscope was inserted without difficulty in three patients. Dilatation of the T tube tract was necessary in one patient in whom the original T tube was only 14 Ch in size; the tract was dilated over a guide wire to 18 Ch without complication and the flexible choledochoscope was then easily inserted

Bile duct clearance was achieved at one sitting in three patients, all of whom had a single stone present on their original T tube cholangiogram. The fourth patient had multiple stones present on the T tube cholangiogram and required four sittings to clear the ducts. Between each sitting, tract patency was maintained with an 18 Ch latex Foley catheter.

Completion tube cholangiograms were performed in two patients. One patient was pregnant at the time of the percutaneous extraction, which precluded radiography. In the other patient, after removal of a single large retained stone, a catheter could not be passed back down the tract and it was assumed that the tract had been disrupted owing to the size of the extracted stone. The patient remained asymptomatic throughout.

Discussion

On discovery of retained common bile duct stones several treatment options are available. Simple flushing of saline may encourage the passage of small stones Dissolution of stones with mono-octanoin may be effective[3], although with any infusion of solvent the flushing effect may contribute to stone removal Methyl-*tert*-butyl ether has principally been used to dissolve gallbladder stones but can be instilled down a T tube[4] although the published results of dissolution are conflicting[5,6]

The two commonly used methods of removing retained stones are removal under fluoroscopic imaging using a steerable catheter and wire basket (Burhenne technique), and endoscopic sphincterotomy with or without Dormia basket stone extraction.

The Burhenne technique has a high success rate, a low complication rate and a negligible mortality rate[7,8]. It can be performed on a day case basis. It has the disadvantages of requiring specialized equipment, including the use of fluoroscopy and radiological expertise which may not always be available. In addition, small stones may be hard to visualize with fluoroscopy but are easily seen with the choledochoscope.

Endoscopic sphincterotomy may be more widely available than facilities for fluoroscopic extraction but there is an overall complication rate of 7–10 per cent and a mortality rate of 0·6–1 5 per cent among all patients undergoing sphincterotomy[2,9,10] The mortality rate may be lower in fitter patients who have previously undergone cholecystectomy, but there is evidence that in those patients who have had recent biliary surgery the complication rate of endoscopic removal of retained stone may be as high as 19 per cent[11]. Although many of these complications are minor there is a small but appreciable incidence of haemorrhage and severe pancreatitis The

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Table 1 *Percutaneous extraction of retained biliary stones via the T tube tract with a flexible choledochoscope*

Series	Year	Cases	Success No (%)
Sherman *et al* [15]	1975	2	2 (100)
Gocho and Hirhesuka[16]	1977	4*	4 (100)
Yamakawa *et al.*[17]	1978	56	54 (96)
Yamakawa *et al.*[17]	1978	23*	20 (87)
Moss *et al.*[12]	1980	17	17 (100)
Hwang *et al.*[18]	1980	30*	25 (83)
Birkett and Williams[19]	1981	22	21 (95)
Ker and Sheen[20]	1981	54*	49 (91)
Jakimowicz *et al.*[21]	1983	73	67 (92)
Choi *et al.*[14]	1986	103	90 (87)
Berci *et al* [22]	1989	100	97 (97)
Weiman *et al* [23]	1989	13	11 (85)
This series	1991	4	4 (100)
Total		501	461 (92)

* Series containing only intrahepatic stones

technique usually requires the cooperation of another hospital department. It is probably inappropriate in patients who still have a T tube *in situ* unless there are particular reasons not to wait the 6 weeks necessary for maturation of the tract.

Percutaneous extraction of retained common bile duct stones via the T tube tract using a flexible choledochoscope may be performed by any surgeon familiar with the flexible choledochoscope. The method uses equipment that should be available to all surgeons undertaking common bile duct exploration and allows stone removal under direct vision. This is particularly helpful if the stones are small.

Some authors recommend insertion of a guide wire before T tube removal[12,13]. We have not found this to be necessary. A 6-week-old tract is a smooth fibrous tunnel through which the choledochoscope will pass easily and usually without steering. It is quite clear when the common bile duct has been entered and from then on the procedure is no more difficult than peroperative choledochoscopy. As with gastroscopy and colonoscopy, successful progress is made by drawing back when the view is lost and rotating the choledochoscope to manipulate the tip rather than excessive angulation with the control wires.

It cannot be overemphasized that surgeons should insert a 16 or 18 Ch T tube after choledochotomy for duct stones. Although the tract may be dilated, this adds considerably to the procedure and probably increases the risk of tract disruption It is also very helpful for the T tube to take a reasonably straight course to the lateral abdominal wall. Intra-abdominal loops may make insertion of the choledochoscope or a steerable catheter difficult or impossible.

The published series of percutaneous choledochoscopies for retained stones are listed in *Table 1*. In 501 cases of retained stones, 461 attained complete duct clearance (92 per cent). The greatest difficulty was encountered in patients with intrahepatic stones In those with stones confined to the extrahepatic biliary tree, success rates of over 90 per cent were usually achieved. Complications were infrequent and usually minor. There have been no procedure-related deaths although one patient in the series of Choi *et al.*[14] died from an incidental myocardial infarct. There should be no additional complications when compared with fluoroscopic extraction as both techniques are basically similar.

Percutaneous choledochoscopic stone extraction has the advantages of being simple to perform and readily available to surgeons Although its use has been described frequently it is not in common use and deserves consideration.

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Gallbladder sepsis after stent insertion for bile duct obstruction: management by percutaneous cholecystostomy

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Of 364 patients undergoing insertion of a biliary endoprosthesis in 1989, six (1·6 per cent) developed gallbladder sepsis. Three patients had cholangiocarcinoma, two had carcinoma of the pancreas and one had a benign biliary stricture. Two of the five patients with malignancy had gallbladder stones, and the patient with a benign stricture developed stones after 3 years of stenting. Three patients developed gallbladder sepsis early after endoprosthesis insertion (<6 days), while in the other three it occurred late (>6 months). All six patients failed to respond to antibiotics and were successfully managed by percutaneous cholecystostomy; the patient with a benign biliary stricture also had cholecystolithotomy. The gallbladder drainage tubes were removed or became dislodged at intervals varying from 2 weeks to 6 months without complications. Percutaneous cholecystostomy is the treatment of choice for gallbladder sepsis unresponsive to antibiotics in patients with a biliary endoprosthesis in situ.

Surgical bypass was previously the principal treatment for bile duct obstruction, but during recent years endoprostheses (stents) have been used increasingly[1]. The results of these two techniques are comparable[2–4], although there is a reduced 30-day mortality rate[3] and decreased inpatient stay[4] for patients treated by stenting. The main problems of stents are well known and include haemorrhage, perforation, pancreatitis and (with time) stent blockage. Other complications are coming to light We report six of 364 patients undergoing insertion of a biliary endoprosthesis at The Middlesex Hospital during 1989 who developed gallbladder sepsis unresponsive to antibiotics with a biliary stent *in situ*. All six patients were successfully managed by ultrasound-guided percutaneous cholecystostomy, thus avoiding the need for surgery.

Case reports

The clinical details are summarized in *Table 1*.

Patient 1 developed cholestatic jaundice in June 1988; endoscopic retrograde cholangiopancreatography (ERCP) showed a hilar stricture with a further stricture of the common bile duct. A 10 Fr endoscopic stent was successfully inserted. Ultrasonography confirmed biliary decompression and showed the gallbladder to be free from stones Percutaneous biopsy showed adenocarcinoma compatible with a diagnosis of cholangiocarcinoma. In September 1988 the patient developed pyrexia with right upper quadrant pain, and ultrasound scanning showed oedema around the gallbladder indicating acute cholecystitis[4]. The cholecystitis was treated with intravenous antibiotics and resolved over the following 72 h Stent changes for blockage were required in January and May 1989, and radiotherapy by external beam and iridium wire was administered in April and May. Recurrent right upper quadrant pain occurred 2 weeks later, with disseminated intravascular coagulation and septicaemia unresponsive to intravenous antibiotics. Ultrasound scanning confirmed acute cholecystitis with oedema around the gallbladder[5] and the presence of local tumour. Under ultrasound control the gallbladder was punctured with aspiration of turbid bile from which *Escherichia coli*, *Streptococcus faecalis* and *Klebsiella aerogenes* were grown on culture. Percutaneous cholecystography showed no flow of dye down the cystic duct and so an 8·5 Fr drain with a Cope loop was positioned in the gallbladder. There was a rapid clinical improvement with only small amounts of serous fluid draining from the gallbladder. The patient was well when discharged 4 days later and the small serous discharge persisted The drain was flushed daily with sterile normal saline, and removed without complication in August 1989. Further stent changes were required in August 1989, January and May 1990, and the patient remains well.

Patient 2 developed jaundice with upper abdominal pain in July 1989 and ERCP showed a type II hilar stricture. Ultrasound showed a hilar mass and multiple gallstones within the gallbladder. Satisfactory biliary drainage was achieved by an endoscopic 7 Fr stent placed in the left hepatic duct, and by combined percutaneous endoscopic procedure a second 11·5 Fr stent was placed in the right hepatic duct. Percutaneous biopsy confirmed cholangiocarcinoma. After stent insertion there was persisting pain associated with pyrexia and rigors despite intravenous antibiotics. Acute cholecystitis was suspected and ultrasound-guided percutaneous gallbladder aspiration revealed pus and therefore the presence of empyema. *E coli* was grown on culture. Cholecystography showed a blocked cystic duct and therefore a 7 Fr Sachs drain was left *in situ*, after which there was a rapid improvement with resolution of the pyrexia and decrease in the level of pain. After 72 h drainage ceased; the drain was left *in situ* on open drainage, flushed regularly with saline, and removed 3 weeks later without complication There was one episode of possible cholangitis, which resolved with antibiotics, and the stent draining the left lobe was changed by a further combined percutaneous endoscopic procedure in January 1990 The patient remains well.

Patient 3 developed cholestatic jaundice in February 1989 ERCP showed a hilar stricture and brush cytology showed cholangiocarcinoma. A 10 Fr endoscopic stent was successfully inserted. Ultrasonography demonstrated a localized hilar mass, but at laparotomy there were multiple metastases and the tumour was not resectable. The gallbladder was free from stones. The stent became blocked in August and at ERCP after stent removal a balloon occlusion cholangiogram (carried out to delineate the biliary anatomy) resulted in contrast medium entering the gallbladder. There was marked tumour progres-

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Table 1 *Clinical details, management and patient outcome*

Patient	Age (years)	Sex	Diagnosis	Gallbladder stones	Timing of gallbladder sepsis	Outcome
1	52	M	Hilar and CBD cholangiocarcinoma	No	Late (11 months)	Drain removed after 3 months, patient alive and well
2	66	M	Hilar cholangiocarcinoma	Yes	Early (2 days)	Drain removed after 3 weeks; patient alive and well
3	48	F	CHD cholangiocarcinoma	No	Early (3 days)	Drain removed after 2 months; patient died after 3·5 months
4	69	M	Carcinoma of the pancreas	Yes	Late (7 months)	Drain dislodged after 1·5 months; patient died after 2·5 months
5	50	F	Carcinoma of the pancreas	No	Early (5 days)	Drain dislodged after 6 months; patient died after 7 months
6	55	F	Benign hilar and CHD stricture	No*	Late (4 years)	Patient alive and well; no stone recurrence at 1 year

CBD, Common bile duct, CHD, common hepatic duct. * Gallbladder stones developed after stenting for 3 years and recurrent cholecystitis occurred during the next year. The stones were removed by percutaneous cholecystostomy under general anaesthetic

sion, with stricturing spreading from the hilum to involve the common bile duct. A further stent was positioned with difficulty in the right hepatic duct. Right upper quadrant pain and a swinging pyrexia developed 48 h later despite postprocedural antibiotics. Ultrasound-guided aspiration produced 200 ml of pus, indicating empyema, and a cholecystogram showed that the cystic duct was compressed with very little flow of contrast medium into the bile duct. A drain was left *in situ* and transiently produced a small amount of serous fluid. The drain was left on open drainage, flushed with saline each day, and removed 2 months later without complication. The second stent blocked soon afterwards and it was not possible to replace it at ERCP owing to further tumour growth. Imaging confirmed extensive tumour and further intervention was not thought to be indicated. The condition of the patient deteriorated and she died 6 weeks later.

Patient 4 developed obstructive jaundice in August 1988, and investigation showed adenocarcinoma of the head of the pancreas. Two stones were seen in the gallbladder by ultrasonography. An endoscopic 10 Fr stent was successfully inserted. Increasing doses of opiate analgesia were required for pain control. Stent change was required in January 1989, and imaging at this time showed tumour progression. In March the patient was admitted with severe right upper quadrant pain and tenderness refractory to large doses of opiate analgesia. He was apyrexial and had a normal white cell count, but ultrasound scanning showed an empyema with a stone impacted in Hartmann's pouch. This was confirmed by percutaneous cholecystogram and a 5 Fr Sachs drain was positioned in the gallbladder with drainage of 250 ml of pus. There was immediate pain relief, and the drainage volume decreased to zero over the next 72 h The Sachs drain was replaced by a 12 Fr Cope loop drain, which was left on open drainage with regular saline flushing, and the patient was discharged home. The drain became dislodged 6 weeks later and fell out. The resulting mucous fistula discharged small amounts of serous fluid and was satisfactorily managed by application of a colostomy bag. The patient deteriorated and death occurred 4 weeks later.

Patient 5 presented with upper abdominal pain, and a mass in the head of the pancreas suggestive of carcinoma was seen by ultrasound scanning. ERCP showed an irregular stricture of the pancreatic duct compatible with this diagnosis. However, percutaneous ultrasound-guided biopsy of the mass showed inflammatory changes only. Jaundice developed 1 month later and ultrasound scanning showed biliary obstruction with a distended gallbladder and no stones. Endoscopic stent insertion failed and therefore a percutaneous transhepatic stent was positioned across the stricture. A percutaneous drain was left *in situ* for 24 h and was then removed after cholangiography had shown good flow of contrast medium through the stent. The patient's condition then deteriorated, with upper abdominal pain and swinging pyrexia despite postprocedural antibiotics. Ultrasound scanning showed an empyema which was confirmed by percutaneous gallbladder puncture. Cholecystography showed an obstructed cystic duct, and the gallbladder was drained externally via a 7 Fr Sachs drain. There was a mixed growth on culture, including *Candida albicans.* Pyrexia persisted and a separate subhepatic collection was seen on repeat ultrasound scanning. This was drained by a further percutaneous 7 Fr Sachs drain. The pyrexia then resolved, both drains were replaced by larger 12 Fr drains on open drainage, which were both flushed regularly, and the patient was discharged. The subhepatic drain was removed 4 weeks later. The patient failed to attend outpatients for a period of 4 months, but was then reviewed. There had been continued weight loss, pain was controlled by opiate analgesia, and drainage had ceased. Ultrasound scanning showed that the pancreatic mass had considerably increased in size. Arrangements were made to remove the gallbladder drain 4 weeks later, but it became dislodged the day beforehand without any untoward effects. The patient's condition deteriorated, and she died 6 weeks later.

Patient 6 had an idiopathic portal vein thrombosis as a child. She remained well until 1984 when she developed jaundice. Investigation showed benign stricturing at the confluence of the right and left hepatic ducts and common hepatic duct, established secondary biliary cirrhosis, portal hypertension and subhepatic varices. The gallbladder was free from stones. She was managed by endoscopic stent insertion with resolution of jaundice, and underwent elective stent change every 4–6 months. In April 1986 for the first time several stones and fragments were seen within the gallbladder by ultrasound scanning, and from 1987 she had several episodes of right upper quadrant pain and pyrexia typical of cholecystitis. Cholecystectomy was contraindicated by the established cirrhosis and portal hypertension and therefore the gallbladder stones were removed by percutaneous cholecystostomy under general anaesthesia. This was complicated by a localized gallbladder perforation, which resolved without further intervention. A 10 Fr Foley catheter was left *in situ* for 1 week with the balloon inflated to 20 ml, and then removed without any subsequent problems. The patient has had no further abdominal pain and so far has not developed further gallbladder stones.

Discussion

At the Middlesex Hospital over 1100 ERCP examinations are carried out annually and the majority of these procedures are therapeutic. In 1989 there were 364 stent insertions, and hence six cases of gallbladder sepsis represents an incidence of 1·6 per cent.

A biliary stent may be associated with gallbladder sepsis for several reasons:

1. Bacterial colonization of bile occurs after endoscopic sphincterotomy[6], which is usually carried out before stent insertion in our practice. In addition, bacteria adhere to plastic, and are therefore invariably present on a stent in the bile duct[7]
2. Impairment of gallbladder function caused by a stent traversing the origin of the cystic duct and causing partial or complete occlusion.
3. Local tumour progression with compression or occlusion of the cystic duct, although this is not directly related to the presence of a stent and could occur after a surgical cholecystenterostomy
4. Gallbladder filling with non-sterile contrast medium during ERCP and stent insertion.
5. Impaired gallbladder function resulting in stasis and the development of gallbladder stones with the consequent risk of cholecystitis or biliary colic.

Thus more than one factor may contribute to gallbladder pathology in individual patients In most of our patients it was not possible to determine their relative importance.

The pathogenesis of gallbladder sepsis is influenced by the length of time that the stent has been *in situ*. Early gallbladder sepsis (within days of stent insertion) is probably due to gallbladder filling with non-sterile contrast medium at stent insertion, combined with impaired gallbladder emptying due either to the stent or to tumour Late gallbladder sepsis (weeks or months after stent insertion) will usually result from tumour growth causing cystic duct compression. Patient 6 in our series is highly unusual, both by virtue of having a benign bile duct stricture not due to previous cholecystectomy, and by not being suitable for surgery because of cirrhosis and portal hypertension. The few patients with benign bile duct strictures managed by endoscopic stenting rather than by surgery rarely have a gallbladder *in situ*. Although such patients are at risk of developing gallstones by virtue of their cirrhosis[8], the timing of the appearance of stones in our patient suggests that impaired gallbladder function due to the stents was also of importance.

There are only two reports of acute cholecystitis attributable to a biliary stent Huibregtse and Tytgat[9] reported a patient who developed acute cholecystitis 6 months after stent insertion for biliary obstruction due to a pancreatic carcinoma in which cystic duct occlusion by tumour was probably the principal cause. Leung *et al.*[10] reported a case of acute cholecystitis after endoscopic stent insertion (also for carcinoma of the pancreas) in which filling of the gallbladder by contrast medium occurred. A total of eight reported cases and an incidence of less than 2 per cent indicates that gallbladder sepsis is an unusual complication of biliary stenting However, it is important for three reasons.

First, early gallbladder sepsis usually results from filling with contrast medium contaminated with gut bacteria during its injection through the ampulla of Vater at ERCP. Although not proven, gallbladder sepsis may be minimized or even prevented by our policy of injecting above a stricture the least amount of dilute contrast medium that is necessary to allow successful stent insertion. In those patients in whom it is not possible to establish endoscopic drainage, the risk of cholangitis is likely to be related to the volume of dye injected above the stricture. A similar argument applies to filling of the gallbladder by contrast medium and the risk of cholecystitis if emptying is impaired.

Second, the diagnosis may not be clinically apparent. Signs of gallbladder sepsis may be mistaken for signs of biliary sepsis due to stent blockage or non-function, sepsis elsewhere in the body, or progression of the underlying disease. Even when suspected clinically, the development of empyema may not be shown by imaging, and gallbladder puncture may be required

Third, and of most importance, effective non-surgical treatment of gallbladder sepsis is available if antibiotics alone are unsuccessful. Ultrasound-guided percutaneous cholecystostomy is the treatment of choice for acute acalculous cholecystitis, and its use in acute calculous gallbladder sepsis in association with lithotripsy is increasing[11–13]. The present series of patients shows that it is an ideal treatment for gallbladder sepsis associated with a biliary stent where only temporary drainage is required, even if gallbladder stones are present The alternative treatments of surgical cholecystostomy or cholecystectomy are contraindicated by the poor prognosis of most patients and the technical difficulty posed by operating in the presence of local and often extensive tumour.

In summary, we describe six cases of gallbladder sepsis in patients with biliary stents *in situ* unresponsive to antibiotics and managed by percutaneous cholecystostomy.

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Influence of cholecystectomy on symptoms

A group of 292 consecutive patients underwent cholecystectomy for gallstones with presumed biliary pain over a 4-year period and all completed a self-assessment questionnaire before operation. Over the following 2 years 18 patients died but no others were lost to follow-up. The remaining 274 patients completed a further questionnaire 1 and 2 years after operation. Demographic characteristics and abdominal symptoms have been compared with an age- and sex-matched control group using the same questionnaire. Before operation symptoms of flatulent dyspepsia were far more frequent in patients with gallstones but operation markedly reduced these symptoms to an incidence which almost matched that of the control group. However, 1 year after cholecystectomy 34 per cent of patients still suffered some abdominal pain and of 35 patients referred back to hospital for investigation none has been shown to have a retained bile duct stone at a minimum follow-up of 5 years. A multivariate analysis indicated that preoperative flatulence together with long duration of attacks of pain are risk factors for postoperative dissatisfaction as judged by a linear analogue scale. However, both these factors are common and neither is a good discriminator of a poor outcome. The prediction of a poor symptomatic outcome after cholecystectomy from preoperative symptoms or patient characteristics had only limited success and all patients should be warned of this risk.

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Cholecystectomy is an accepted treatment for the complications of gallstones and for biliary pain. However, the relationship between gallstones and the spectrum of symptoms described as flatulent dyspepsia is uncertain[1] and it is therefore difficult to advise patients with these symptoms what the outcome of surgery is likely to be. The symptoms of flatulent dyspepsia were described by Johnson[1] as: repeated belching, full feeling after a normal sized meal, inability to finish a normal sized meal, the abdomen becomes blown out so that clothes have to be loosened, burning in the upper abdomen, burning discomfort in the chest (heartburn), bitter fluid regurgitation into the mouth, vomiting or nausea.

We have conducted a cohort study of all patients undergoing cholecystectomy on one firm at a District General Hospital over a 5-year period. Comparisons have been made with data collected from an age- and sex-matched control group admitted to the same hospital. The aim of the study was to clarify the effects of cholecystectomy upon symptoms in order that patients might be better counselled preoperatively.

Patients and methods

Between July 1980 and April 1985, 295 consecutive patients undergoing cholecystectomy on one firm of the William Harvey District General Hospital, Ashford, Kent were asked to complete a self-assessment questionnaire preoperatively. They completed the questionnaire again on the anniversary of their operation 1 and 2 years later. The criteria for cholecystectomy were gallstones with upper abdominal pain which was considered to be of biliary origin or the presence of complications No patient had a cholecystectomy for asymptomatic gallstones or for flatulent dyspepsia alone and patients were warned that all their symptoms might not be relieved The questionnaire recorded demographic characteristics and the type, duration and frequency of abdominal pain and the presence of gastrointestinal symptoms

The questionnaires recorded all nine symptoms described by Johnson[1] but for the purpose of evaluation the following five categories were analysed flatulence (belching), reflux-type indigestion, distension, nausea and vomiting. The postoperative questionnaire also included a linear analogue scale on which the subject recorded their perception of the success of cholecystectomy.

From February 1984 to August 1987, 278 patients admitted for elective surgery at the same hospital were asked to act as controls and complete the same preoperative questionnaire. In order to be eligible, individuals must not have had a history of biliary disease or a diagnosis of any condition likely to produce abdominal symptoms Controls were matched by sex and for age by decade. Body Mass Index (BMI = weight in kg/height in metres^2) was calculated for all gallstone and control subjects.

A copy of the questionnaire is available on application to the authors. The questionnaire data were entered into a 'Simple' database on a Prime 2655 computer (Prime UK Ltd , London, UK). Statistical analysis was performed using BMDP version April 1985 (BMDP Statistical Software, Los Angeles, California, USA).

Results

No patient refused to co-operate in the study or join the control group but three patients were too ill to complete the preoperative questionnaire and they all died in the early postoperative period. No patient was lost to follow-up over the 2-year period but in the first year one patient died of postoperative haemorrhage, seven of malignancy and six of cardiac, vascular or respiratory disease. In the second year there were four further deaths from malignancy. Control and cholecystectomy subjects appeared well-matched for demographic features (*Table 1*), except that the gallstone patients were slightly heavier and had a higher BMI than the control group The gallstone patients were more likely to designate themselves as housewives and gave a family history of gallstones more frequently.

The classical description of the gallstone patient is the fat, fair, fertile, flatulent, female in the forties or fifties[2–4] but only 22 per cent fell within this age–sex range and had been pregnant. Flatulence (belching), distension and reflux-type indigestion were approximately twice as common in patients with gallstones

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Table 1 *Characteristics of gallstone and control groups*

	Control $n=278$	Gallstone* $n=278$	Significance‡
Mean age (range)	52·8(21–95) (s.e. 0·94)	53·3(20–90) (s.e. 0·94)	
Male/female	82/196	82/196	
Never married	22	22	
Pregnancies	2·27(0·12)	2·58(0·13)	n.s.
Height (cm)	167 (0·6)	164 (1·0)	$P=0{\cdot}01$
Weight (kg)	66·3(0·73)	67·3(0·78)	$P=0{\cdot}28$
Body Mass Index (weight/height^2)	23·4(2·14)	24·5(2·65)	$P=0{\cdot}001$
Social status			
Professional	6	4	
Intermediate	24	19	
Skilled	116	90	
Unskilled	8	10	
Housewife†	92	126	$P=0{\cdot}01$
Smoker	182	178	n.s.
Under 2 units alcohol daily	224	222	n.s.
Family history of gallstones	45	70	$P=0{\cdot}01$
Oral contraceptive use	77	70	n.s.

*The gallstone group consists of all cholecystectomy patients who survived to complete a self-assessment questionnaire 1 year later, †Statistical analysis refers to females only, housewife *versus* others, ‡t test or χ^2 test with Yates continuity correction, one degree of freedom, used, n.s., not significant

Table 2 *Symptoms recorded by gallstone patients compared with control group*

	Control subjects $n=278$	Gallstone patients Pre-op $n=278$	1st year post-op $n=278$	2nd year post-op $n=274$
Flatulence	30	66	44	42
Distension	33	57	37	40
Indigestion	38	71	43	42
Nausea	15	62	23	19
Vomiting	10	54	9	10
Fever	4	34	5	4
Rigor	4	30	5	2
Abdominal pain	Nil	100	34	27
Consulted general practitioner for pain	Nil	100	23	18

Values are percentages

than in controls (*Table 2*). Nausea and vomiting were four to five times as frequent but postoperatively the frequency of symptoms fell to near the levels reported by controls and there was little difference between the groups at 1 and 2 year follow-up. At 1 year, one-third of patients still had abdominal pain and one-quarter had consulted their general practitioner for this symptom.

The linear analogue scale recordings of the perceived success of the operation (*Figure 1*) show that the cholecystectomy patients had very similar results at both one and 2 years postoperatively. From these results it was arbitrarily decided that a patient scoring less than nine on the linear analogue scale considered their operation less than a total success.

A univariate analysis was performed on the results obtained from the questionnaires to determine which characteristics or symptoms were associated with the operation being considered less than a total success. Patients with preoperative flatulence (belching) ($P<0{\cdot}01$), distension after meals, reflux-type indigestion or an alcohol intake of less than 2 units ($P<0{\cdot}05$) more commonly have an unsuccessful outcome than those without these symptoms. However, the sex of the patient, the number or severity of previous attacks judged by patient scoring, previous hospital admissions or the need for exploration of the common bile duct did not affect the symptomatic outcome.

Multivariate analysis was performed using stepwise logistic regression (*Table 3*). Preoperative flatulence and long versus short duration of attacks of pain appeared to predict a poor outcome and patients over 55 seemed to fare worse than younger patients Persistence of abdominal pain postoperatively was associated with a poor symptomatic outcome and this also applied to recurrence of flatulence, nausea, fever and reflux-type indigestion.

A total of 35 patients were referred back to hospital by their general practitioners and underwent investigation of their persisting postoperative symptoms These records were reviewed in October 1990 at a minimum of 5 years

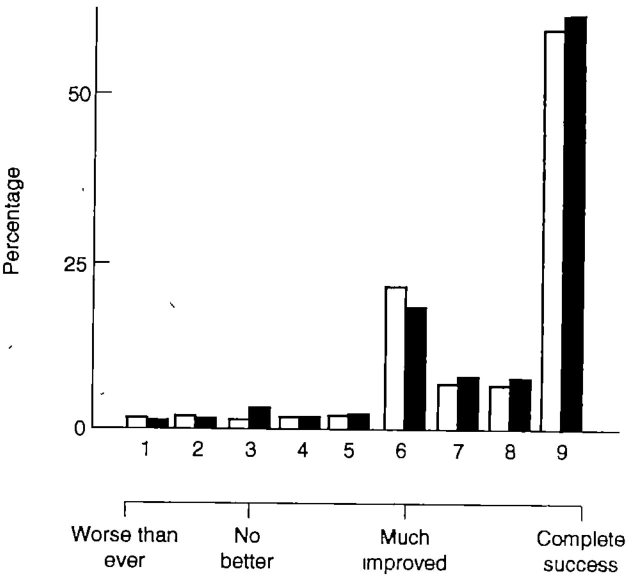

Figure 1 *The perception of success of cholecystectomy* □, *1st year;* ■, *2nd year*

Table 3 *Factors found to be significantly associated with cholecystectomy being considered less than a complete success multivariate analysis*

Characteristic	Percentage affected ($n=278$)	Percentage of affected considering operation less than total success	Significance*
Preoperative			
Flatulence	66	47	$P=0{\cdot}002$
No flatulence	34	28	
Duration of pain			
Days or weeks	33	49	$P=0{\cdot}05$
Hours	67	37	
Age			
Under 55 years	47	36	$P<0{\cdot}02$
Over 55 years	53	45	
Postoperative			
Persistent pain	34	77	$P<0{\cdot}001$
No pain	66	22	
Flatulence	44	64	$P<0{\cdot}001$
No flatulence	56	23	
Nausea	23	75	$P<0{\cdot}001$
No nausea	77	30	
Fever	5	87	$P<0{\cdot}05$
No fever	95	38	
Indigestion	43	57	$P<0{\cdot}05$
No indigestion	57	28	

Values are percentages; *multivariate analysis

Table 4 *Final diagnoses made in patients investigated for persistent symptoms following cholecystectomy*

Hiatus hernia/reflux	2
Gastritis/peptic ulceration	3
Pancreatic pseudocyst	1
Chronic pancreatitis	2
Renal stone	1
Irritable bowel syndrome	3
Diverticular disease	7
Colitis	2
Wound problems	8
Unknown cause	6
Total	35

postoperatively (*Table 4*). All patients had undergone operative cholangiography and in no case was the biliary tract directly implicated. However, one patient developed a pancreatic pseudocyst and two patients were diagnosed as suffering from chronic pancreatitis at endoscopic retrograde cholangiopancreatography (ERCP).

The bile duct was explored at the time of cholecystectomy in 55 patients (20 per cent), the approach being supraduodenal in 32 and transduodenal in 23. Of the 35 patients referred back to hospital nine (26 per cent) had had an exploration of the bile duct and in seven cases this had been transduodenal. ERCP was carried out in six cases, four of whom had had transduodenal sphincteroplasty; chronic pancreatitis was diagnosed in two of these but no retained stone was found in any case.

Of the 274 patients reviewed at 2 years, 34 had been admitted urgently before cholecystectomy (12 per cent) as had a similar proportion of those with persisting symptoms (three of 35).

Forty-two patients (15 per cent) were operated on originally for complications of gallstones. Twenty-four patients were jaundiced at the time of their index admission and of these seven had cholangitis. Twenty patients had recently had acute pancreatitis and of these two were jaundiced. Of the 35 patients investigated for persistent symptoms 8 (23 per cent) had undergone cholecystectomy because of a complication of gallstones The state of the gallbladder wall was described in the operation note in all but four of the 35 patients with severely persistent symptoms and this was normal in only three (10 per cent).

Discussion

All patients in this consecutive cholecystectomy series had originally experienced moderate or severe upper abdominal pain which was presumed to be biliary in origin. However, a third still had abdominal pain 2 years after operation and although 13 per cent of all patients were referred back to hospital, no retained stone was identified The other unexpected finding was that the symptoms of flatulent dyspepsia were reduced after cholecystectomy to the same incidence as that of the control population.

Biliary pain is presumed to result from mechanical, inflammatory or chemical irritation of the gallbladder but the basis for the other symptoms associated with gallstones remains incompletely understood[5]. The symptom-complex of flatulent dyspepsia is often exacerbated by fatty foods and the gallbladder containing stones may therefore be incriminated as the root of the problem. However, many surgeons have felt that the results of cholecystectomy are uncertain in this situation and advise caution. Two studies have addressed this problem by conducting surveys of middle aged women as the presumed high risk population using either oral cholecystography[6] or ultrasound[7] and two larger studies have looked at men and women[8,9]. Little difference was found in the prevalence of dyspeptic symptoms between those with stones and those without and it has therefore been assumed that cholecystectomy has little effect on these complaints. However, the subjects were not representative of patients who undergo cholecystectomy since few had biliary pain or a complication. All four studies had incomplete compliance and the possibility of selection bias. Jorgensen, in a study of 3600 patients[9] found that a third of subjects with or without gallstones complained of right upper quadrant pain within the last year However, of the 101 subjects who had had a cholecystectomy more than 1 year previously, 56 per cent complained of right upper quadrant pain. None of the control subjects in the present study complained of right upper quadrant pain and it is possible that a selection bias has reduced the incidence of abdominal pain below that experienced by a truly random sample of the population.

It is accepted that an unknown proportion of the control subjects had gallstones but none gave a history of upper abdominal pain. We did not carry out a longitudinal study on the controls but it could be argued that reported symptoms might come and go over a period of time or that individual subjects might respond differently to a repeat questionnaire received at home.

The cholecystectomy patients in the present series are a selected group of the population with gallstones since all had some degree of upper abdominal pain. Furthermore two-thirds of the patients were female and yet the female:male ratio of gallstones in the necropsy population in the same district is less than 2·1[10]. It seems that women with gallstones are more likely to be investigated and referred for cholecystectomy[11] but only one in ten of the UK population with gallstones ever has them removed. The selection of patients for cholecystectomy may be biased toward the group perceived to be most at risk but the present cohort of cholecystectomy patients is representative of those patients a surgeon has to advise preoperatively.

Cholecystectomy patients were shorter and had a greater body mass index than controls but, although these differences were statistically significant, their absolute magnitude was too small to be clinically useful. This unfortunately is the case for most other factors studied. Smoking, alcohol and use of the contraceptive pill were just as common in patients as controls although the better symptomatic outcome in those patients with a significant alcohol intake was unexpected and may be a chance finding due to multiple comparisons. Cholecystectomy patients were more likely than controls to have a first degree relative diagnosed as having gallstones (25 per cent *versus* 16 per cent), but this may be due to recall bias.

Results from linear analogue scales are difficult to interpret and it can be argued that patients scored their operation much improved or better because the design of the form funnelled responses to the right. However, a third still had abdominal pain 1 and 2 years later and it therefore seems valid to group together all patients scoring their operation as less than a complete success.

Thirty-five patients in the present study were investigated for persistent pain but none was found to have a biliary tract cause. All patients had an operative cholangiogram, but postoperative investigations only included ERCP where this was clinically indicated. The results are largely in agreement with two series from the UK investigating postcholecystectomy symptoms with the exception of age effect[1,12] but a high incidence of retained stones has been reported from an ERCP referral centre[13].

Previous studies of symptomatic outcome after cholecystectomy have not looked at a control population. Bodvall and Overgaard[14] followed 1930 patients after cholecystectomy and found that 60 per cent were symptom-free but dyspepsia persisted in 11 per cent and 30 per cent had a degree of pain. Severe symptoms were largely blamed on retained stones and similar results were reported by Stefanini *et al.*[15].

Rhind and Watson[16] directly addressed the question: 'If you take out my gallbladder, shall I lose my indigestion?' Cholecystectomy cured or improved dyspeptic symptoms in over 80 per cent of their 56 patients with gallstones. Gunn and Keddie[17] found that the symptoms reduced from 88 per cent preoperatively to 19 per cent postoperatively in 107 patients.

Preoperative pain was relieved by operation in 77 per cent and improved in a further 16 per cent.

Ros and Zambon have recently examined the persistence of symptoms in 130 patients undergoing elective cholecystectomy but only 93 were available for follow-up[18]. In their study 58 patients had complained of dyspepsia before operation and follow-up on 46 revealed that this had persisted in 22 (48 per cent). This study has been widely interpreted as showing that cholecystectomy does not relieve dyspeptic symptoms but remains appropriate for biliary pain[19,20]. There is no evidence from the present study that poor results were due to retained stones and the commonest cause of the postcholecystectomy syndrome seems to be the result of an operation carried out for the relief of symptoms that were not due to gallstones in the first place

Clinical experience suggests that patients with biliary colic have a better symptomatic outcome than those with more prolonged attacks of pain and the results support this prejudice. It is also shown that preoperative flatulence is a risk factor for postoperative dissatisfaction but both these factors are common and neither is a good discriminator of a poor outcome. It is therefore disappointing that it has not been possible to identify clearly before an operation those patients with presumed biliary pain at high risk of a poor symptomatic outcome who might wish to avoid cholecystectomy[21].

In conclusion, the expectation of some patients that cholecystectomy will relieve dyspeptic symptoms appears to be realistic but the relief is unpredictable[22,23]. One-third of patients continue to suffer pain after cholecystectomy and since it was not possible to identify this group before operation, all patients should be warned of the risk.

Acknowledgements

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Announcement

Association of Surgeons in Training

Membership of the Association is open to all senior registrars holding accredited posts in general surgery, urology, plastic surgery, neurosurgery, orthopaedics, cardiothoracic surgery and paediatric surgery. Registrars in the above specialties who are 2 years post-fellowship may also apply. The Association represents the views of members on all matters relevant to surgical training and also holds scientific and social meetings. If you are not a member please contact the Secretary, Barney Harrison, 6 Kyveilog Street, Pontcanna, Cardiff CF1 9JA, for details of membership, local representatives and forthcoming meetings. The next AGM will be held in Oxford, 19–21 September 1991.

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Non-operative management of blunt liver injuries

Over a 10-year period 281 patients with liver injuries following blunt abdominal trauma were seen at Westmead Hospital. A decision to treat the liver injury without an operation was made in 55 (20 per cent) of the 281 patients. Two of these 55 patients required a subsequent laparotomy, one for continued bleeding and one for a bile leak. No patient died from a missed intra-abdominal or retroperitoneal injury or from concealed haemorrhage. These patients were compared with 181 patients with liver injuries who were operated on. The two groups of patients could be distingushed in terms of their clinical status on arrival at the hospital, the magnitude of their injury and the sequelae of the injury. Non-operative management proved a safe alternative to an operation in appropriate patients, but a laparotomy to exclude unsuspected intra-abdominal injuries is associated with little significant morbidity and offers some reassurance in managing patients with multiple injuries.

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Over the past two decades there has been an increasing trend to the non-operative or so-called 'conservative' management of liver trauma, especially in children[1–6]. The rationale for a selective policy of non-operative treatment of certain liver injuries is based on the observation that between 50 per cent and 70 per cent of liver injuries will have stopped bleeding by the time an operation is performed[6–9]. Of the remainder, some 70–80 per cent require only simple surgical techniques to control haemorrhage[8].

Most series to date have included only selected patients to demonstrate the validity of the conservative approach. The purpose of this study was to determine the place of non-operative management in a large group of patients with blunt liver injuries.

Patients and methods

Data on all patients with liver injuries seen at Westmead Hospital over a 10-year period between 1 February 1979 and 31 January 1989 have been collected prospectively on a database maintained in the Department of Surgery. Information collected included age, sex, clinical condition of the patient, type and mechanism of injury, associated injuries, treatment, investigations and outcome.

The presence of a liver injury was proven either by autopsy, operation or organ imaging – computed tomographic (CT), ultrasonographic or radionuclide scanning. Clinical suspicion alone was regarded as inadequate.

The grade of liver injury was stratified following a previously described method[10]

Grade I	Simple, non-expanding haematomas as demonstrated on ultrasonographic or CT scan
Grade II	Incised stab wounds
Grade III	Low velocity bullet wound
Grade IV	Single blunt split or subcapsular haematoma
Grade V	Devitalization of liver tissue without major bleeding not covered by other classification
Grade VI	Multiple tears in the liver with or without devitalization of parenchyma, but without major hepatic venous injury
Grade VII	Liver injury associated with major venous injury

Shock was considered to be present if the systolic blood pressure was <100 mmHg in the presence of impaired peripheral circulation. The presence of a coagulopathy was defined as at least a 1·5-fold prolongation in the partial thromboplastin time and/or thrombin time or a platelet count of <75 000 per mm^3.

Patients were studied in three groups: (1) those in whom a decision was made to treat the liver injury without an operation, (2) those in whom a laparotomy was performed, and (3) a subgroup of the patients operated on in whom a laparotomy was performed, a liver injury identified but no surgery performed on the liver.

The decision to treat a patient without surgery was made on clinical grounds. Criteria included. (1) the ease and speed of resuscitation, (2) the need for continuing blood transfusion, and (3) haemodynamic stability over 4–6 h. Artificial constraints were not placed on the decision-making process Specific criteria such as the systolic blood pressure, haemoglobin or haematocrit, pulse rate or the results of organ imaging studies were not used to decide whether patients would be included in the non-operative group.

Results

Over the 10-year period of this study 306 patients with liver injuries were treated at Westmead Hospital. Blunt trauma was the most common injury (281 patients), and these patients form the basis of this study Their ages ranged from 1 to 84 years with a median of 23 years. There were 172 (61 per cent) men. Motor vehicles were responsible for 167 (59 per cent) of the 281 injuries. Other common injuries included motor cycles, pedestrian accidents and falls.

Of the 281 patients with blunt liver injuries 181 (64 per cent) were treated by operation at Westmead Hospital and these 181 patients constitute the operated group. The non-operated group consisted of 55 patients in whom a decision was made to manage the liver injury without an operation. Of the 45 remaining patients, 11 had definitive operations elsewhere, 32 had the diagnosis of liver injury made at autopsy and two were referred with haemobilia for embolization of the hepatic artery. These 45 patients have been excluded from further analysis.

The definitive diagnosis was made by organ imaging, usually CT scan, in 69 patients. In three patients, with liver injuries subsequently proven at laparotomy, CT scanning failed to identify a small liver laceration.

The median age of the non-operated group was 15 years (range 1–78 years), compared with a median of 25 years for the operated group (range 2–81 years). Thirty of the 55 in the non-operated group were aged ⩽16 years as were 30 of the 181 in the operated group (χ^2 30·105, $P<0·001$).

Table 1 shows that of the 55 patients treated without operation ten were shocked on arrival, eight were unconscious and the abdomen was distended in five. In comparison, 79 of the 181 patients treated by operation were shocked (χ^2 10·586, $P=0·001$), 82 were unconscious (χ^2 15·637, $P<0·001$) and 50 had a distended abdomen (χ^2 7·103, $P=0·007$). The median number of associated injuries incurred by the non-operated group was one with a range of zero to six, 29 patients incurring

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Table 1 *Comparison of clinical parameters in patients treated with and without operation*

Parameter	Without operation ($n = 55$)	With operation ($n = 181$)	P
Shock	10	79	0·001
Unconsciousness	8	82	<0·001
Distended abdomen	5	50	0·007
Associated injuries <2	29	34	<0·001
Coagulopathy	2	64	<0·001
Grade of injury <IV	5	82	<0·001
Hospital stay <15 days	29	19	<0·001
<2 units of blood	28	16	<0·001
ISS <30	26	27	<0·001
Died	1	57	<0·001

P value obtained using χ^2 test. ISS, injury severity score

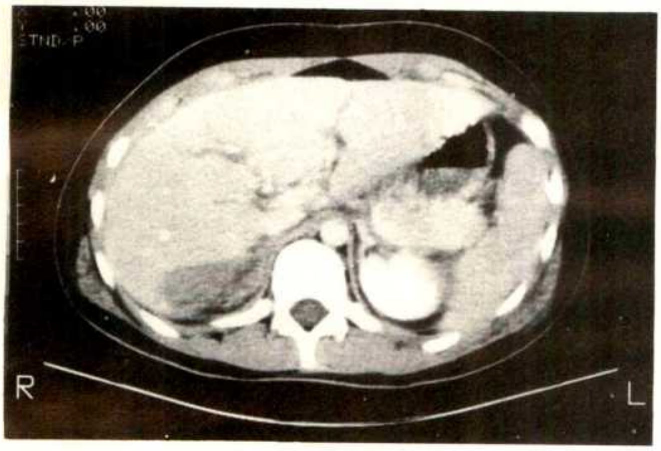

Figure 1 *Subcapsular haematoma. This is a grade IV injury*

fewer than two associated injuries. In comparison, the median for the operated group was three, with a range of zero to eight injuries, only 34 of 181 incurring fewer than two injuries (χ^2 23·131, $P<0·001$). The liver injuries incurred by the non-operated group were also of a lower grade. Five of the non-operated group sustained major (one grade V and four grade VI) injuries (*Figures 1–3*). Eighty-two of the 181 patients in the operated group sustained major injuries (χ^2 22·237, $P<0·001$). There were two grade V injuries, 44 grade VI injuries and 36 grade VII injuries.

A coagulopathy developed in two patients treated without operation and in 64 of the operated group (χ^2 19·527, $P<0·001$). Patients treated without an operation required a median of one unit of blood (range 0–15 units), compared with a median of nine units for those treated by operation (range 0–102). Fewer than two units of blood were required by 28 of the non-operated group whereas all but 16 patients in the operated group required two or more units (χ^2 46·484, $P<0·001$).

One of the patients treated without operation died from a head injury. Of the 181 patients needing an operation 57 died, 30 from blood loss (χ^2 18·469, $P<0·001$). The non-operated group spent a median of 13 days in hospital (range 3–100 days) while the operated group spent a median of 31 days (range 6–265). Twenty-nine of the non-operated group spent <15 days in hospital compared with 19 days in the operated group (χ^2 43·86, $P<0·001$).

An injury severity score (ISS) was calculated routinely on all patients after January 1985. It was calculated for 39 of the 55 patients treated without an operation, with a range of 4–75 and a median of 25. The ISS was <30 in 26 of these 39 patients. Of the 181 patients treated by operation an ISS was calculated for 111. It ranged from 13 to 75 with a median of 41. The ISS was <30 in 27 of the 111 patients (χ^2 20·83, $P<0·001$).

Two patients initially treated without operation subsequently required an operation, one as a result of continued bleeding from a liver laceration. The second patient required an operation 72 h after admission for an unrecognized bile leak. A further patient became suddenly hypotensive 6 days after admission. A CT scan demonstrated a ruptured subcapsular haematoma. The patient was transfused with three units of blood and did not require a laparotomy. Those patients who underwent surgery recovered from their operations without complications. There was no morbidity or mortality as a result of an undiagnosed intra-abdominal or retroperitoneal injury in

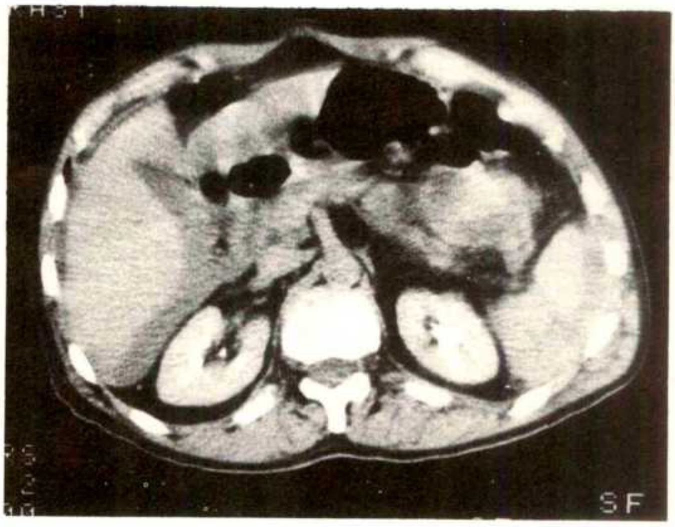

Figure 2 *CT scan of liver demonstrating a grade VI injury: two deep lacerations across the liver substance and a subcapsular haematoma*

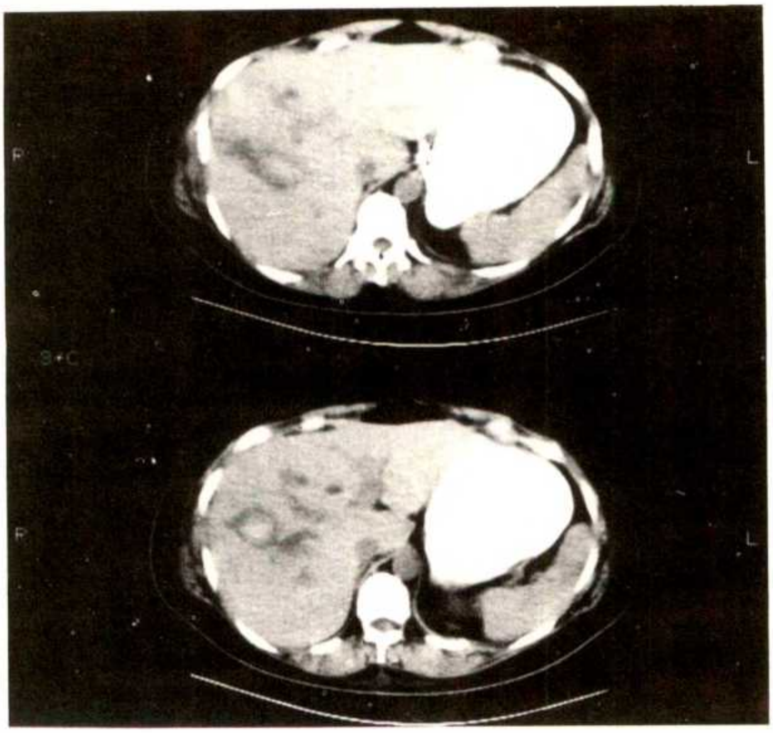

Figure 3 *Extensive bilobar liver injury with multiple lacerations and intrahepatic haematoma (grade VI injury)*

Table 2 *Comparison of clinical parameters in patients treated without operation and those treated by surgery with no procedure to the liver*

Parameter	Without operation ($n=55$)	Non-therapeutic ($n=55$)	P
Shock	10	18	0·122
Unconsciousness	8	21	0·009
Distended abdomen	5	13	0·068
Associated injuries <2	29	4	<0·001
Coagulopathy	2	5	0·441
Grade of injury >IV	5	3	0·675
Hospital stay <15 days	29	7	<0·001
<2 units of blood	28	10	0·001
ISS <30	26	12	0·009
Died	1	8	0·035

P value obtained using χ^2 test. ISS, injury severity score

either group. No patient treated without operation developed intra-abdominal sepsis or haemobilia.

Fifty-five of the 181 patients in the operated group underwent a laparotomy at which a liver injury was seen, but no procedure to the liver was performed. Of these 55, 42 had significant associated intra-abdominal or retroperitoneal injuries requiring surgery. The indications for operation in these patients were splenic injury in 14, retroperitoneal injury including injury to the pancreas, kidney or bladder in 16, torn mesenteric vessels in five, hollow viscus injury in three, ruptured diaphragm in two and bile duct injury in two. Of the 16 with retroperitoneal injuries, ten had a positive peritoneal lavage and 15 had three or more associated injuries. The 13 patients without abdominal or retroperitoneal injuries all had significant chest, head or bone injuries. The indication for operation in these 13 patients was based on a positive peritoneal lavage in ten, CT diagnosis of a liver injury in two and clinical status of the patient in one. Comparison between these 55 patients and those patients not undergoing surgery is shown in *Table 2*. Patients undergoing laparotomy sustained significantly more severe injuries, measured by unconsciousness, number of associated injuries and ISS. Those undergoing laparotomy sustained more complications, had a longer hospital stay, a greater transfusion requirement and higher mortality rate. The most common complication was chest infection in 33 patients. No patient had long-term morbidity as a result of their laparotomy.

Discussion

The non-operative treatment of blunt liver injuries has been shown to be safe both in children[1–6] and in patients with intrahepatic haematoma[11–17]. Recent reports have indicated that this approach is applicable to adult patients[18–21].

We have avoided surgery in 20 per cent of patients with blunt liver injuries. It was not possible to identify specific criteria, such as systolic blood pressure, haematocrit or CT findings, by which patients can be selected for non-operative management. Indications for surgery seemed to be: (1) evidence of gross blood loss (>40 per cent of blood volume), (2) evidence of continuing blood loss during resuscitation, and (3) diagnostic doubt about the extent of blood loss or possible injury to other intra-abdominal structures as may be seen in multisystem injuries or neurotrauma.

When the present data were analysed, patients treated without an operation could be distinguished from those managed by operation by the following criteria: (1) clinical status: they were less likely to be shocked, unconscious, coagulopathic or have abdominal distension, (2) injury severity: the magnitude of the injury was less, with fewer associated injuries, a lower grade of liver injury and a lower ISS, and (3) sequelae of injury: the hospital stay was shorter, the complication rate was lower and there was a lower transfusion requirement.

There was also a significant difference in the age of the patients, those treated without an operation being younger. This difference probably reflects the greater acceptance of non-operative treatment by paediatric surgeons rather than a difference in the type of patient in whom non-operative management is appropriate.

There were similar but less marked differences (for five parameters still significant) between patients treated without operation and those who had a laparotomy but no liver surgery (*Table 2*). In both groups of patients the majority of liver injuries were of low grade (grade I–IV). The significant difference was in the extent of the associated injuries as seen in the number of unconscious patients, the number of associated injuries and the ISS. Consequently, patients operated on had a significantly higher transfusion requirement and a longer hospital stay.

At this hospital, patients who are clinically stable on arrival have a CT scan rather than a diagnostic peritoneal lavage or urgent laparotomy. If the CT scan demonstrates a liver injury, we do not use specific CT criteria as outlined by other authors[19–21] to determine the need for an operation; cardiovascular status and abdominal signs form the basis of decision making. However, accurate and easily available organ imaging is essential if patients are to be managed without operation to define clearly not only the liver injury, but any associated injuries. CT scanning also allows the clinician to follow the progress of the injury as it resolves and enables early detection of potential complications. An enlarging haematoma, persisting haemoperitoneum and periportal collections of blood or bile may represent potential complications[20,22]. Whether we should place more emphasis on CT findings in deciding whether to perform an operation is not answered by this study. Both patients who needed laparotomies after an initial decision to avoid surgery had CT scans fulfilling accepted criteria for continued non-operative management[19–21]. Furthermore, we have successfully managed without operation three patients who were haemodynamically stable throughout their hospital stay, despite CT scan evidence of extensive bilobar lacerations and intraperitoneal blood (*Figures 2* and *3*).

Of the 55 patients treated without operation in this study, two required an unplanned laparotomy and one died from a head injury 48 h after admission. The incidence of unplanned laparotomies was similar to that in other series[18,19]. Non-operative management may fail in the early stage because of continued bleeding or a bile leak[6,18–20], or late because of ruptured haematoma[13] or sepsis in and around devitalized parenchyma[23,24].

Non-operative treatment of blunt abdominal trauma has failed to gain universal acceptance. This reflects concern about the potential risk of continued haemorrhage and unsuspected intra-abdominal or retroperitoneal injury[6]. CT scanning has not reduced the incidence of non-therapeutic laparotomy[25] because of uncertainty about its sensitivity in identifying liver injuries[26,27] and injuries to other intra-abdominal and retroperitoneal structures[25–30]. In patients with multiple injuries it seems reasonable to operate to determine the exact abdominal injuries and to ensure that any bleeding is controlled.

Laparotomy at which no treatment was necessary for the liver injury was performed in 55 (30 per cent) of the 181 patients who were operated on in this series. Only 13 of these 55 patients did not require surgery for injury to an intra-abdominal or retroperitoneal structure; none of the 13 died or suffered long-term morbidity as a result of the laparotomy. This is consistent with previous work[31,32] demonstrating that a laparotomy is not associated with mortality, and that long-term morbidity is uncommon[31]. Minor morbidity, especially chest infection, is common after operations for blunt abdominal trauma, and this risk is further increased if there is a large number of associated injuries[31,32]. While a chest infection may prolong the hospital stay, its sequelae are insignificant when compared, for example, with those of a missed pancreatic or duodenal injury.

This series has reaffirmed the validity of a selective policy of non-operative management of liver injury. Patients may be managed without operation with minimal mortality and a low morbidity rate. The most important decision facing a clinician is to distinguish between patients who need an operation and those in whom an operation may be avoided. Unstable patients need an operation. Patients who are stable on arrival or those who respond quickly to fluid resuscitation may be managed without operation, but should have a CT scan to identify the extent of the liver injury, the presence of associated retroperitoneal and intra-abdominal injuries and to provide a baseline so that resolution of the injuries may be observed. Patients with extensive injuries to other organ systems, particularly the chest, abdomen and retroperitoneum, should probably have a laparotomy even if they are clinically stable. Most surgeons will accept that not all appendicectomies are therapeutic. Perhaps this dictum should be applied to trauma. A laparotomy to exclude concealed haemorrhage and unsuspected intra-abdominal injury is associated with little significant morbidity and offers some reassurance in managing patients where multiple body systems are injured.

Non-operative management is only an option, it is not an alternative to an operation when the latter is indicated, and it will not reduce the mortality rate associated with liver injury.

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Case report

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Mediastinal transfixion with a crossbow bolt

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Case report

A 24-year-old man shot himself in the chest with a crossbow bolt following a domestic argument (*Figure 1*). After 16 min he was admitted by ambulance to the Accident and Emergency Department, alert, orientated, complaining of severe chest pain, but haemodynamically stable. The heel of a crossbow bolt projected from a midline entry wound 5 cm above the xiphoid process. There was venous congestion of the upper trunk. His pulse rate was 120 per min and blood pressure was 110/50 mmHg. Chest examination revealed no evidence of haemopneumothorax or surgical emphysema. Chest radiography showed the bolt traversing the mediastinum, apparently traversing the heart and impaled in the tenth thoracic vertebra, with no radiological evidence of haemopneumothorax. The patient was sedated with intravenous opiates. Surgery was deferred for 55 min until full cardiopulmonary bypass facilities, including consultant anaesthetist, experienced cardiothoracic surgeons, technical staff and crossmatched blood, were available. The patient remained stable throughout.

Initial vascular access for cardiopulmonary bypass was secured via femorofemoral cannulation following which a median sternotomy was performed, skirting the entry site. There were 100 ml of blood in the pericardial sac. The bolt was found to pass through the middle of the lower sternum, the anterior wall of the right ventricle and to emerge from the posterior wall of the left ventricle 2 mm lateral to the posterior interventricular artery just below the atrioventricular groove, before passing through the posterior pericardium (*Figure 2*). Subsequently aortobicaval cannulation was performed and cardiopulmonary bypass with profound hypothermia (10–15°C) and intermittent circulatory arrest was employed. The bolt was found to traverse the interventricular septum just below the septal cusp of the tricuspid valve and posteriorly had transfixed the descending thoracic aorta before embedding in the vertebra. As access to and control of the descending thoracic aorta would have proved difficult laterally, the aorta was exposed through the posterior pericardium. Following removal of the bolt the defects in the aorta were joined, effectively creating a complete transection. Repair by primary end-to-end anastomosis was facilitated by short periods of circulatory arrest. The ventricular wall and ventricular septal injuries were repaired with non-absorbable mattress sutures placed over Teflon® (E.I. du Pont de Nemours and Co., Wilmington, Delaware, USA) pledgets. Postoperative recovery was uncomplicated with no evidence of cerebral or spinal cord ischaemia and the patient discharged himself on the eighth postoperative day. He remains asymptomatic 6 months after surgery.

Discussion

Most patients with penetrating injury to the heart die before reaching hospital from exsanguination, cardiac tamponade or extensive myocardial contusion[1]. Among those reaching hospital alive or with recent signs of life, the prognosis is worse for patients with bullet wounds given that stab wounds tend to cause less tissue destruction[2]. Left ventricular and multiple chamber injuries have a particularly poor outlook[3]. Ventricular septal defects occur in about 1 per cent of cases[2].

Crossbow and arrow wounds to the mediastinum are very unusual causes of penetrating chest injury and represent a form of impalement injury. Impalement injuries involving the great vessels are usually rapidly fatal but in some arrow wounds the weapon acts as its own obturator, snugly plugging the defect

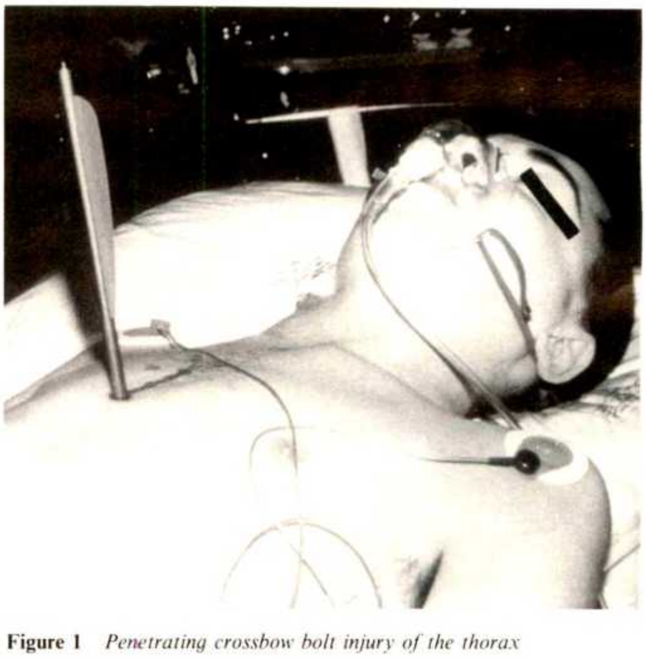

Figure 1 *Penetrating crossbow bolt injury of the thorax*

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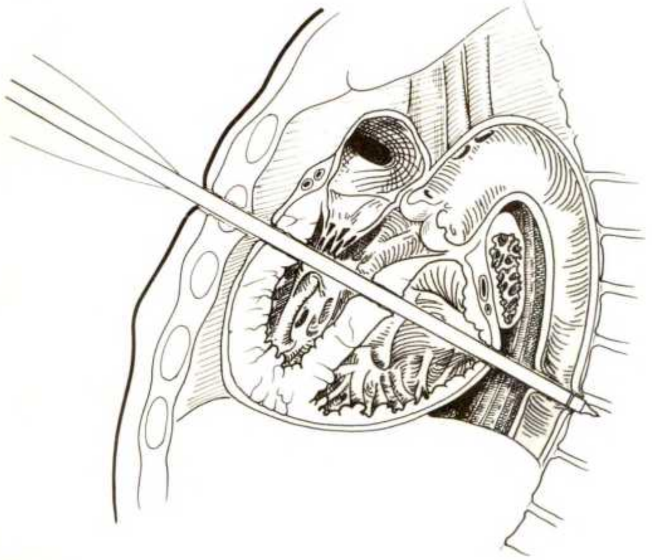

Figure 2 *Trajectory of the bolt causing transfixion of the myocardium and descending thoracic aorta*

and preventing exsanguination. There are reports of patients remaining in a stable cardiovascular condition for hours and even days before receiving medical attention[4]. Conversely, withdrawal of the penetrating object outside hospital, or even by inexperienced surgical staff under inappropriate conditions, may lead to torrential and fatal haemorrhage. Young, fit patients tolerate moderate hypotension which can be accepted pending immediate surgery, provided pulse and blood pressure are stable. Over-aggressive transfusion may simply increase bleeding from ventricular or arterial wounds.

Penetrating heart wounds rarely require cardiopulmonary bypass for surgical correction but in the present case survival would have been most unlikely without such facilities because of the aortic transfixion. Our patient's preoperative condition was so stable and the predictable injuries so severe that transfer from a more peripheral unit could have been considered had it been necessary. This is in contrast to the more usual penetrating stab wounds to the heart where the weapon has been withdrawn and cardiac tamponade develops rapidly. Urgent anterolateral thoracotomy may be necessary and should not be postponed in a rapidly deteriorating patient because of lack of bypass facilities[5].

Acknowledgements

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Accurate intraoperative transhepatic U tube placement

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Cholangiocarcinoma of the main hepatic duct junction is best treated by curative resection, although this is not often possible as most lesions are associated with local infiltration, portal vein invasion or metastases. For unresectable lesions, we advocate the use of a wide bore U *tube followed by radiotherapy. Placement of the* U *tube must be accurate and meticulous. This paper describes a simplified method allowing accurate intraoperative transhepatic* U *tube placement.*

While curative resection is the optimal treatment for cholangiocarcinoma of the main hepatic duct junction, this is seldom possible since most lesions are associated with local infiltration, portal vein invasion or metastases. When an unresectable lesion is present, either left duct or segment III duct hepaticojejunostomy or operative intubation after dilatation are the preferred palliative treatment options[1]. Our group has advocated the use of a wide bore U tube followed by radiotherapy[2], and this technique remains our treatment of choice because other forms of therapy have not been proved to be superior[3]. Endoscopic intubation becomes increasingly difficult as the distance between the ampulla and the tumour increases. Patients with a high bile duct lesion may survive for relatively long periods so that endoscopically or percutaneously (radiologically) placed small-lumen endoprostheses frequently become blocked, giving rise to cholangitis.

The success of the U tube procedure demands meticulous and accurate placement of the tube after tumour dilatation. This report describes a simplified method allowing accurate intraoperative transhepatic U tube placement.

Insertion of the U tube

After cholecystectomy the common bile duct is explored through a longitudinal choledochotomy 3 cm below the cholangiocarcinoma at the main hepatic duct junction. Diagnostic material for histology or cytology is obtained by choledochoscopy. The next step is careful dilatation of the lesion. A Teflon-coated® (E.I. du Pont de Nemours and Company, UK) Lunderquist-Ring biliary torque control guidewire (Cook Inc., Boomington, Indiana, USA) is advanced through the stricture into the right intrahepatic duct guided by an angiographic catheter using intraoperative C arm fluoroscopy. The stricture is initially dilated over the guidewire with a 7-Fr coaxial catheter and then dilatation is sequentially increased using a 4-mm diameter 7-Fr Gruntzig balloon catheter (Cook Inc.). Careful dilatation over the guidewire avoids creating a false passage, and care should be taken not to split the tumour and produce a biliary leak. Once adequate dilatation has been achieved, careful intraoperative right intrahepatic duct cholangiography is performed to define the intrahepatic biliary anatomy and select the appropriate right anterior segmental duct to allow maximal intrahepatic duct utilization. The guidewire/catheter combination is passed through the selected duct as far peripherally as possible on the low anterolateral surface of the liver to avoid injury to a major hepatic vein and the inconvenience presented by the costal margin. The stiff end of the guidewire is passed through the duct, liver parenchyma and capsule. The Gruntzig balloon catheter is passed over the guidewire and through the duct wall, parenchyma and liver surface after making a 1-cm incision in Glisson's capsule. The tract through the parenchyma is gently dilated with the Gruntzig balloon sufficiently to accept passage of the 16-Fr large-bore Levin-type Argyle U tube (Sherwood Medical Industries Ltd, UK) (*Figure 1*). The relation of the planned side holes to the tumour is carefully assessed and two side holes are cut in the tube, one situated above the lesion and the other below the lesion in the common bile duct. In practice, these holes are sited approximately 3 cm apart depending on the size of the lesion. The tube holes are cut through the radio-opaque marker line for later radiological identification. The Gruntzig balloon tip is inserted into the prepared U tube, and the balloon inflated and tied in place to secure the U tube which is railroaded and drawn back through the tract and into the anterior right major duct and through the previously dilated stricture (*Figure 2*).

The cholangiocarcinoma and the upper limit of the

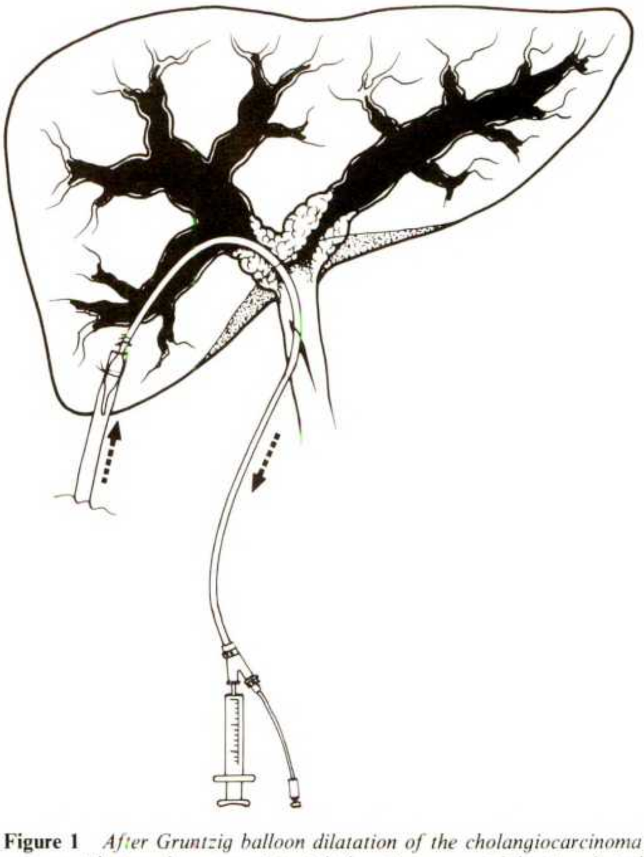

Figure 1 *After Gruntzig balloon dilatation of the cholangiocarcinoma over a guidewire, the appropriate right hepatic segmental duct is selected by intraoperative fluoroscopy. The* U *tube is secured to the end of the balloon catheter and drawn back through the tumour*

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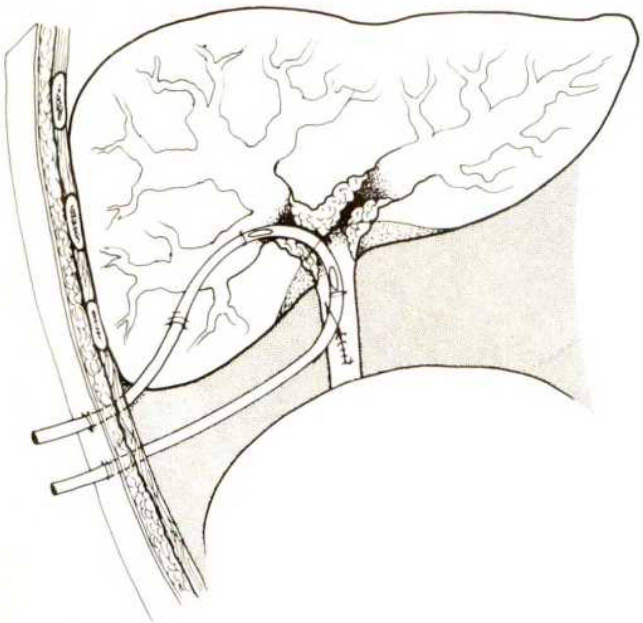

Figure 2 *The* U *tube is positioned with side holes above and below the lesion. Both limbs of the tube exit through the abdominal wall without intra-abdominal slack*

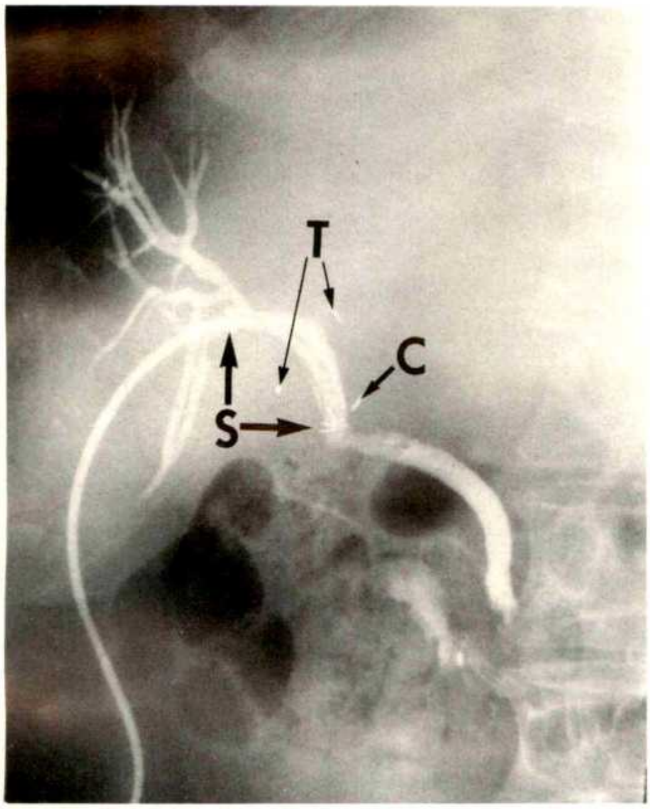

Figure 3 *The site of the tumour* (*T*) *and choledochotomy* (*C*) *are marked with silver clips and the position of the tube side holes* (*S*) *identified by silver wire markers*

choledochotomy are marked with silver clips to aid accurate fluoroscopic positioning of the U tube and subsequent iridium wire placement (*Figure 3*). The choledochotomy is repaired around the tube with interrupted sutures, and the ends of the tube are brought through the abdominal wall via separate stab incisions, cut to a suitable length and positioned comfortably to avoid kinking. The best method of tube fixation is to connect the limbs at skin level without intra-abdominal slack using a transversely placed cross-piece (*Figure 4*). The tube should not be sutured directly to the skin since the sutures will inevitably pull out and lead to tube displacement and bile leakage[4]. The position of the cross-piece relative to the abdominal wall should make allowance for breathing and bending, and should be carefully checked as the liver size reduces after relief of biliary obstruction. The cross-piece may require adjustment with repositioning closer to the anterior abdominal wall. Postoperatively the accurate positioning of the U tube is confirmed radiologically by contrast study (U tubogram). Latex rubber tubing is used to connect the two external ends of the tube, converting the U tube to a circle or O tube (*Figure 4*). After 6 weeks, the stiffer Argyle U tube is replaced by railroading a softer Silastic U tube (Dow Corning, Reading, UK) into position. The new tube is attached to a limb of the old tube with stout thread and the old tube extracted, pulling the new tube into position. The holes in the old tube provide a template for precise placement of the side holes in the new tube which are marked with silver wire. Accurate positioning of the tube's silver wire markers relative to the cholangiocarcinoma and choledochotomy silver clips ensures correct positioning of the tube side holes. The lower silver wire marker on the U tube should remain above the choledochotomy clip to ensure that the lower U tube side hole remains within the bile duct (*Figure 3*).

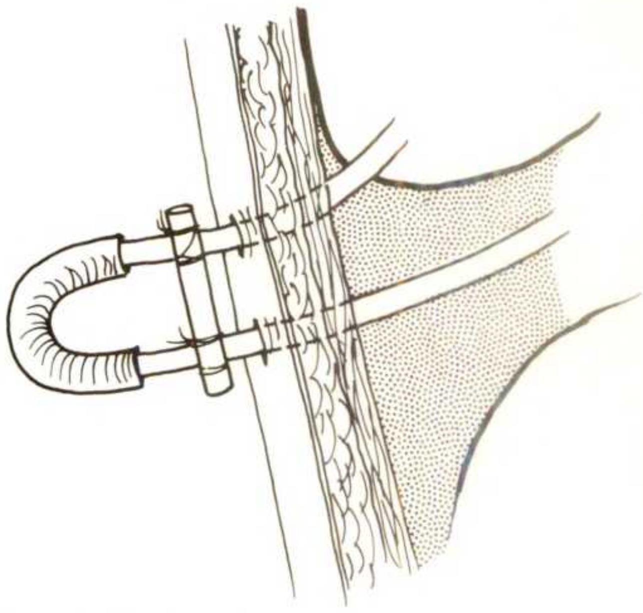

Figure 4 *The* U *tube ends are connected by latex rubber tubing and secured using a transversely placed cross-piece*

Acknowledgements

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Distal pancreatectomy with and without splenectomy

Splenectomy is performed routinely during distal pancreatectomy, yet the spleen has an important role in host defence and can often be preserved. A personal series of 100 distal pancreatectomies undertaken for pancreatic disease between 1978 and 1990 included 23 patients undergoing total pancreatic resection. The remaining 77 patients, who form the basis of the present report, underwent primary distal pancreatectomy and comprised 34 women and 43 men with a median age of 41 years (range 17–78 years). Conventional distal pancreatectomy including splenectomy was performed in 42 patients (55 per cent) for chronic pancreatitis (34 patients), pancreatic neoplasia (six patients), suspected pancreatitis (one patient) or pancreatitic trauma (one patient). Conservative resection with splenic preservation was performed in 35 patients (45 per cent) for chronic pancreatitis (12 patients), suspected pancreatitis (13 patients, including eight patients with pancreas divisum), pancreatic neoplasia (six patients), recurrent acute pancreatitis (two patients) and pancreatic trauma (two patients). There were no postoperative deaths in either group. Early complications followed conventional resection in 10 patients (24 per cent) and conservative resection in seven patients (20 per cent). In five patients the splenic vessels were ligated away from the splenic hilum and the spleen was left in situ, *but subsequent isotope scans and haematological indices showed no hyposplenism. The spleen can safely be preserved in many distal pancreatic resections, including those for inflammatory disease, and we now prefer a retrograde technique for dissecting the pancreas off the splenic vessels.*

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The intimate relationship of the splenic artery and vein to the body of the pancreas makes splenectomy a routine part of distal pancreatectomy, especially in patients with inflammatory disease[1]. The spleen, however, is an important organ in the immunological defence of the host[2–4] and is worthy of preservation if this can be safely achieved. The techniques of spleen-preserving distal pancreatectomy, though logical in the paediatric patient, have not been extensively applied in adults except in the context of pancreatic trauma[5,6]. Since the publication of our early results of conservative distal pancreatectomy[7], our experience has increased to include some patients with chronic pancreatitis, while our technique has also evolved.

We present a series of 77 distal pancreatectomies, 42 conventional and 35 conservative. The word 'conservative' is used to imply sparing of the spleen rather than limited excision of the pancreatic tissue itself.

Patients and methods

Between April 1978 and September 1990, 77 patients underwent distal pancreatectomy for a variety of pancreatic diseases, excluding those who had distal pancreatectomy as part of a radical resection for gastric cancer. Conventional distal pancreatectomy was performed in 42 patients and conservative resection in 35. They comprised 34 women and 43 men of median age 41 years (range 17–78 years).

Although patients were not randomized to one or other operation, we have tried to compare the postoperative outcome of each procedure. The two groups were reasonably well matched for age and sex, but clearly patients with more advanced chronic pancreatitis tended to undergo conventional distal resection.

Conservative resection

Indications. An attempt at conservative distal pancreatectomy was considered in three particular situations. First, in 'diagnostic' caudal pancreatectomy where the objective was a limited (20–30 per cent) distal resection to secure pancreatic tissue for histological examination and to obtain a prograde pancreatogram. This procedure was carried out in the early years of this series in patients with suspected pancreatitis, several of whom had pancreas divisum. All patients had a history strongly suggestive of chronic pancreatitis, but extensive investigations had proved inconclusive. If endoscopic retrograde cholangiopancreatography (ERCP) was also inconclusive or unobtainable (cannulation of the accessory papilla may be difficult in pancreas divisum), it was felt justifiable to proceed to on-table prograde pancreatography which is often successful in those situations where ERCP has failed[8]. Second, conservative distal pancreatectomy was considered in patients with disease localized to the pancreatic tail, such as those with neuroendocrine tumours; and third, in patients with chronic pancreatitis in whom atrophy and sclerosis of the body and tail of the gland had caused it to 'shrink away' from the splenic vessels and allow a dissection plane to be developed. This disposition could only be established at operation following a trial dissection.

Patients. Conservative distal pancreatectomy was carried out in 35 patients comprising 16 men and 19 women of median age 43 years (range 17–78 years). Operation was performed for benign tumours in five patients and pancreatic trauma in two (*Table 1*). One patient underwent conservative distal pancreatectomy and left hepatic lobectomy for a malignant neuroendocrine tumour with hepatic metastases. Of 27 patients explored for chronic abdominal pain, 12 were known to have pancreatic disease (chronic pancreatitis), and the remainder had severe and persistent symptoms that were suggestive of chronic pancreatitis. These 15 patients included eight with pancreas divisum, two with recurrent acute pancreatitis and one with a benign ductal stricture. The character of the pain, the absence of any other lesion on detailed investigation of the upper abdomen and, in some cases, the surgeon's findings at a previous laparotomy, raised the suspicion of pancreatic disease. We had either failed to obtain a dorsal pancreatogram endoscopically or the images obtained were non-diagnostic.

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Table 1 *Conservative (spleen-preserving) distal pancreatectomy: indications and outcome in 35 patients*

Indication		Number of patients	Follow-up (range)	Outcome
Chronic pancreatitis		12	2 months–7 years	Pain relief in eight
Recurrent acute pancreatitis		2	1 year and 3 years	No further attacks
Suspected pancreatitis		13		
Pancreas divisum	8		1–4 years	Pain relief in four
Ductal stricture	1		2 years	Pain relief
No cause found	4		2–15 months	Pain relief in two
Neoplasia		6		
Gastrinoma	1		4 years	Died of carcinomatosis
Insulinoma	2		2 years and 8 years	Alive and well
Cystadenoma	1		2 years	Alive and well
NFE 'benign'	1		2 months	Alive and well
NFE malignant	1		2 years	Died of carcinomatosis
Pancreatic trauma		2	4 years	Alive and well

NFE, Non-functioning endocrine

Table 2 *Conventional distal pancreatectomy (with splenectomy): indications and outcome in 42 patients*

Indication		Number of patients	Follow-up (range)	Outcome
Chronic pancreatitis		34	1–12 years	Pain relief in 20
Neoplasia		6		
Adenocarcinoma	2		2 months and 2 years	Died of carcinomatosis
NFE 'malignant'	2		2 months and 1 year	Alive and well (with liver metastases)
Cystadenocarcinoma	1		1 year	Lost to follow-up
Schwannoma	1		10 years	Alive and well
Obscure abdominal pain		1	11 years	Pain relief
Pancreatic trauma		1	7 months	Alive and well

NFE, Non-functioning endocrine

Operative technique. The prograde dissection technique used during the first part of the study period has already been described[9]. We have now largely replaced this with an alternative technique, commencing at the level of the neck or proximal body of the pancreas (depending upon the planned extent of resection) A plane is developed between the pancreas in front and either the splenic vein or the superior mesenteric and portal veins behind. Once 2–3 cm of pancreas has been freed, the gland is divided using a Kocher's director to protect the great veins. Retrograde dissection is now continued towards the spleen, securing the pancreatic branches of the splenic artery and vein as before. The splenic vessels can often be seen grooving the posterosuperior aspect of the pancreas

Whichever technique is employed, there is an opportunity to perform prograde pancreatography[8] before the transected duct is under-run and the pancreatic stump is oversewn with 3/0 silk sutures. The spleen is inspected before closing the abdomen, and drains are placed in the pancreatic bed.

Conventional resection

Indications Conservative distal pancreatectomy was considered contraindicated in patients with pancreatic cancer, splenic vein thrombosis, pseudocyst, gross calcification or severe inflammation. Conventional distal pancreatectomy was performed in such patients with no attempt to preserve the spleen Splenectomy was also carried out in a few cases of injury to the splenic artery or vein during a trial dissection

Patients Conventional distal pancreatectomy with splenectomy was undertaken in 42 patients comprising 27 men and 15 women of median age 41 years (range 20–75 years) Thirty-four patients underwent resection for chronic pancreatitis limited to the distal gland, i e. with relative sparing of the head Six patients had malignant tumours, one had suspected pancreatitis and one had a late resection for pancreatic trauma, having already undergone splenectomy at the initial emergency laparotomy (*Table 2*)

Operative technique. The operation was performed in standard fashion as described elsewhere[9], with the recent modification that we now prefer to perform the dissection in a retrograde rather than a prograde direction.

Results

Conservative resection

The extent of the pancreatic resection varied from 20 to 70 per cent (median 30 per cent). The stump of the transected pancreas was oversewn in all patients except one with chronic pancreatitis and a pseudocyst, in whom an onlay pancreaticojejunostomy was performed to the dilated duct in the head. In five patients, the splenic artery was ligated because of bleeding, and in three of these the splenic vein was also ligated. Division of the artery was carried out close to the point of pancreatic transection, or at least away from the splenic hilum, and the spleen appeared viable and was not removed. Postoperative haematological screening showed neither thrombocythaemia nor Howell-Jolly bodies (i e. no evidence of hyposplenism), and radionuclide scans obtained in three patients showed normal uptake of isotope by the spleen.

The two insulinomas, the gastrinoma and the benign non-functioning islet cell tumour were found to be solitary with no overt metastases The 12 patients with known pancreatic disease had histological changes of chronic pancreatitis, as did six of the 15 patients with chronic abdominal pain; the remaining nine patients had a negative laparotomy and normal pancreatic histology.

Postoperatively, two patients developed a peripancreatic collection detected by ultrasound. One resolved spontaneously and the other was drained percutaneously Two patients developed adhesion obstruction of the small bowel requiring laparotomy at 10 days and 50 days. One patient developed a delayed wound infection 3 weeks after discharge from hospital. One pancreatic fistula presenting through the abdominal drain closed spontaneously at 35 days. Another patient who underwent both highly selective vagotomy for a chronic duodenal ulcer and conservative distal pancreatectomy for chronic pancreatitis had a long and complicated postoperative course. A pancreatic fistula presenting through the abdominal drain healed after 21 days, but the patient was readmitted 1 month later with partial rupture of a false aneurysm of the splenic artery requiring emergency splenectomy, which was complicated by a gastric fistula. Postoperative complications occurred in seven patients (20 per cent), therefore, but there were no deaths. The outcome of these patients is summarized in *Table 1*.

Conventional distal pancreatectomy

The extent of the pancreatic resection varied from 30 to 70 per cent (median 50 per cent). The stump of the transected pancreas was oversewn in 38 patients, and in four (including one with a pseudocyst) an onlay pancreaticojejunostomy was performed. In 37 patients, conventional distal resection was the planned procedure, but in five patients (all of whom had chronic pancreatitis) splenectomy had to be performed after attempts at a conservative resection had failed. In four of these five, dissection of the splenic vessels from the pancreas had to be abandoned because they were too adherent to a severely inflamed and scarred gland, while in the fifth the pancreatic tail actually lay posterior to the vessels at the splenic hilum, making further dissection impossible.

Three patients had a reactive haemorrhage within the first 24 h and needed immediate reoperation. Four patients developed peripancreatic collections, which were drained percutaneously under ultrasound control. One patient developed a pancreatic fistula through the drain, which closed spontaneously at 1 month. One patient developed a faecal fistula, which required reoperation and closure. Another patient with severe chronic pancreatitis who underwent emergency distal pancreatic resection for recurrent gastrointestinal haemorrhage (following pseudocystgastrostomy and subsequent Polya gastrectomy at another hospital) had a stormy postoperative course. The patient developed a gastric fistula on the fifth day and later bled from an aneurysm of the coeliac axis, which was managed by transcatheter embolization. The gastric fistula required surgical closure, and the patient was eventually discharged from hospital 4 months after the distal pancreatectomy. Postoperative complications occurred in 10 patients (24 per cent), therefore, but there were no in-hospital deaths. The outcome of these patients is summarized in *Table 2*.

Discussion

Our results show that distal pancreatectomy can be performed safely without sacrificing the spleen in a variety of pancreatic conditions, including chronic pancreatitis. The spleen was conserved in 45 per cent of all distal pancreatectomies and in 40 per cent of those with proven pancreatic disease. This goal cannot be achieved without strict selection of patients, and the indications and contraindications have altered over the last 12 years in the light of our increasing experience with this procedure. We do not attempt conservative pancreatectomy when there is gross pancreatic calcification or when marked oedema and fibrosis encase the splenic artery and vein alongside the pancreatic tail. Thus for severe chronic pancreatitis we believe that conventional distal pancreatectomy including splenectomy remains the appropriate procedure.

Our operative technique for conservative distal resection has also evolved. The early experience, which included several limited resections for pancreas divisum, involved left-to-right (prograde) dissection of the pancreas. As we have increasingly attempted splenic conservation in patients with chronic pancreatitis, we now generally prefer to divide the pancreatic neck at the start of the operation and peel the gland back towards the spleen in a retrograde fashion. If the splenic artery does have to be divided in a difficult case, the spleen is likely to survive on its arterial supply from the vasa brevia and gastroepiploic arcade provided the site of ligation is outside the splenic hilum.

The technique of spleen-preserving distal pancreatectomy is not new. It was first described by the French surgeon Mallet-Guy[10] in the 1940s in patients undergoing distal pancreatectomy for chronic pancreatitis. More recently, Warshaw[11] has described a technique whereby the splenic artery and vein are deliberately divided distal to the tail of the pancreas, almost within the splenic hilum. We feel that it is unnecessary to divide the splenic vessels and prefer to maintain arterial and venous continuity, even though this is a slightly more time-consuming procedure.

In our series, no patient died in hospital or within 30 days of operation in either the conventional or the conservative group. Pancreatic leaks occurred in four of our patients following conservative distal pancreatectomy and in five patients following conventional resection. They appeared either as peripancreatic collections seen on ultrasound or as a pancreatic fistula presenting via an abdominal drain. Collections were successfully treated by percutaneous drainage under X-ray control, but the three pancreatic fistulas prolonged hospital stay by 3–4 weeks. Several other patients with an uneventful recovery had high concentrations of amylase detected from abdominal drains.

Management of the pancreatic stump is an unresolved problem in our opinion. Routine drainage into a Roux-en-Y loop of jejunum has been recommended by some surgeons[12–14], but Shankar and co-workers[1] have shown, in a large retrospective study, that lateral pancreaticojejunostomy confers no benefit in terms of reducing the incidence of pancreatic fistula. Their overall incidence of pancreatic fistula was identical to ours (five of 113 or 4·4 per cent *versus* three of 77 or 3·9 per cent). Stapling of the pancreatic remnant has become popular in the USA[15–19], but this technique and the more recently introduced procedure of pancreatic 'banding'[20] (which is associated with a 9 per cent incidence of pancreatic fistula) require further evaluation. Since Roux-en-Y pancreaticojejunostomy adds to the length of the operation and does not reliably prevent the problem of leakage, it should probably be reserved for those patients with a dilated duct and/or stricture in the head of pancreas.

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Case report

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Tumours of the liver, bile ducts, pancreas and duodenum in a single patient with familial adenomatous polyposis

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The distribution of tumours in the upper gastrointestinal tract in patients with familial adenomatous polyposis parallels mucosal exposure to bile[1]. The presence of duodenal, pancreatic, bile duct, gallbladder and liver tumours in a patient with polyposis is reported here.

Case report

A 78-year-old male with familial adenomatous polyposis presented with a 12-month history of weight loss and a 2-month history of epigastric abdominal pain The patient had undergone colectomy and ileorectal anastomosis at 41 years of age. Upper gastrointestinal endoscopy revealed Stage IV duodenal polyposis[1]. The largest adenoma was 15 mm in diameter and was next to the papilla of Vater Abdominal ultrasonography revealed a 2-cm mass in the head of the pancreas and multiple hypoechoic lesions in the liver. Computed tomographic-guided biopsy of the liver showed the presence of adenocarcinoma. The patient developed obstructive jaundice and died 7 weeks later.

Post mortem findings

The liver was studded with numerous nodules. The common bile duct contained two tumours. The first, just below the junction of the right and left hepatic ducts, caused obstruction. The second tumour was 3 cm above the ampulla. Underlying the latter lesion was a hard, 3-cm mass within the head of the pancreas with proximal pancreatic duct dilatation. The gallbladder was thickened and had an irregular mucosal surface. Lymphadenopathy was present in the porta hepatis, above the pancreas and around the aorta. The adrenal glands contained nodules. The oesophagus contained numerous sessile oesophageal polyps (<0·7 cm in diameter). The second and third parts of the duodenum contained five polyps (<1·5 cm in diameter), and the rectal stump contained two polyps (<0·8 cm in diameter). The stomach, jejunum and ileum did not contain polyps.

Histology revealed the presence of primary adenocarcinomas in the liver, gallbladder, common bile duct and pancreas, with adjacent dysplasia in each organ. Secondary deposits of adenocarcinoma were found in the porta hepatis nodes and within an adrenal cortical adenoma. The oesophageal polyps were not adenomas; they showed acanthotic stratified squamous epithelium with glycogenic vacuolation Moderate dysplasia was found in the villous adenomas in the duodenum and rectum.

Discussion

Reports of primary tumours occurring in areas exposed to bile in patients with familial adenomatous polyposis include cancers in the duodenum[2], gallbladder[3], bile ducts[4] and liver[5]. Dysplasia in the duodenum, gallbladder, bile ducts and main pancreatic duct in a patient with familial adenomatous polyposis and carcinoma *in situ* of the ampulla of Vater and of the common bile duct has also been described[6].

This is the first report of primary cancers in the liver, gallbladder, bile ducts and pancreas in a single patient with polyposis. The presence of extensive dysplasia of the pancreatico-biliary-duodenal epithelium in association with multiple discrete invasive adenocarcinomas suggests a field change in mucosa exposed to bile, and supports speculation that bile plays a role in tumour development in patients with polyposis.

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Pancreatic pseudocysts: a proposed classification and its management implications

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Pancreatic pseudocysts in 83 patients were classified according to clinical and radiographic criteria. Group I (45 patients) had acute, 'post-necrotic' pseudocysts with normal pancreatic duct anatomy and rarely duct–pseudocyst communication. Percutaneous drainage was curative in all patients in whom it was used. Group II (26 patients) included 'post-necrotic' pseudocysts developing in patients already suffering from chronic pancreatitis. The pancreatic duct was diseased but not strictured, and duct–pseudocyst communication was often present. Percutaneous drainage is possible for such patients but it may have to be prolonged; surgical internal drainage was usually successful. Group III (12 patients) had chronic 'retention' pseudocysts. The pancreatic duct was grossly diseased and strictured and duct–pseudocyst communication was present in all cases. Percutaneous drainage is contraindicated and surgical internal drainage has a high recurrence rate. Operative procedures in this group should address the specific ductal pathology. An improved classification of pseudocysts could help the surgeon to choose the most appropriate form of treatment.

Pancreatic pseudocyst is the most common complication of pancreatic inflammatory disease. The so-called acute pseudocyst[1] is usually an acute peripancreatic fluid collection which resolves spontaneously in the vast majority of cases. Conversely, chronic pseudocysts rarely resolve spontaneously; they present with a well established wall and are therefore amenable to immediate internal drainage. While classification into acute and chronic types may help decide the timing of surgical intervention, this does not take the underlying disease into account. Acute pseudocysts occur in acute pancreatitis but can develop in chronic pancreatitis after an acute exacerbation. Chronic pseudocysts are usually associated with chronic pancreatitis but may develop after an episode of acute pancreatitis. From the anatomical point of view, pancreatic pseudocysts are either intrapancreatic or extrapancreatic, but this is of little help in management decisions.

The exact mechanism leading to pseudocyst formation has not been established completely, but prevailing opinion holds that there are at least two different pathogenic processes involved, and that this may produce two different types of pseudocyst. The first occurs in acute pancreatitis and results from a process of autodigestion with extravasation of pancreatic juice into the lesser sac, pancreas or retroperitoneum[1,2]; it can be termed a 'post-necrotic' pseudocyst. The second occurs in chronic pancreatitis. It is related to ductal obstruction and increased intraductal pressure leading to localized rupture of the pancreatic duct or ductules, with extravasation of pancreatic juice and subsequent pseudocyst formation[2–4]. The type may be termed a 'retention' pseudocyst. Post-necrotic cysts can develop in patients with chronic pancreatitis who suffer from an acute attack; in this situation they may be indistinguishable from their counterpart in acute pancreatitis.

Based on review of the literature and our own clinical experience, we now propose an improved classification of pancreatic pseudocysts into post-necrotic type I, post-necrotic type II, and retention or type III. This study examines the potential importance of this classification as a determinant of management and outcome.

Patients and methods

Prospective documentation of patients with pancreatic pseudocysts admitted to this institution between January 1983 and June 1990 was undertaken. The majority of patients (78 cases) were admitted directly to this department with acute or chronic pancreatitis. Five patients with established pseudocysts were referred from other hospitals. Patients with acute peripancreatic fluid collections, without evidence of encapsulation on ultrasonography or at operation, were excluded, as most of these collections resolve within 1–2 weeks. Seventy of the 83 patients were men and their ages ranged from 17 to 65 years (mean 39 years). The pancreatitis was alcohol-associated in 58 patients (70 per cent), due to blunt abdominal trauma in 18 patients (22 per cent), and in seven patients (8 per cent) the aetiology was uncertain. Gallstone disease is rare in the population treated in this hospital.

Fifty-two patients had acute pseudocysts of less than 4 weeks' duration (34 of group I and 18 of group II, see below), and 31 patients had chronic pseudocysts (11 of group I, 8 of group II and 12 of group III; see below). The diagnosis of pseudocyst was made in all patients by ultrasonography. Computed tomography (CT) scans with oral and intravenous contrast agent were obtained in 46 patients (55 per cent). In the first 4 years of the study CT scanning was performed when the ultrasonographic findings were equivocal or when complications were suspected. From 1987 CT scans have been performed routinely in all patients thought to have severe or complicated pancreatitis. Endoscopic retrograde cholangiopancreatography (ERCP) was performed in all patients with chronic pancreatitis, and in ten patients with acute pancreatitis once the acute phase had settled.

The patients were divided into three groups (*Table 1*). Group I comprised 45 patients with post-necrotic pseudocysts associated with acute pancreatitis, 40 per cent of them had traumatic pancreatitis. Although alcoholic pancreatitis may be regarded as a chronic disease, those patients who presented with their first attack and who had no radiological evidence of chronic disease were included in this group. Group II comprised 26 patients with post-necrotic pseudocysts associated with chronic pancreatitis in whom ERCP demonstrated no obstruction of the pancreatic duct. Group III comprised 12 patients thought to have retention pseudocysts.

The patients were initially managed by withholding oral intake and giving intravenous fluids and analgesia as long as they had continuing abdominal pain, vomiting or ileus. If treatment was required for more than 5 days, total parenteral nutrition was instituted.

Every patient with a diagnosis of pancreatic pseudocyst had several ultrasound studies to monitor the evolution of the cystic collection. Pseudocysts were managed conservatively for approximately 4 weeks from the time of their presumed formation, unless complications

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Table 1 *Proposed classification of pseudocysts*

	Post-necrotic (type I)	Post-necrotic (type II)	Retention (type III)
Presentation	Acute	Acute on chronic	Chronic
Underlying disease	Acute pancreatitis	Chronic pancreatitis	Chronic pancreatitis
Pseudocyst wall	Immature/ mature	Immature/ mature	Mature
Location of pseudocyst	Extrapancreatic	Mostly extrapancreatic	Mostly intrapancreatic
Communication with duct	Rare	Sometimes	Always
ERCP findings	Normal duct	Abnormal duct but no stricture	Ductal stricture

occurred During the early years of the study, management decisions were left to the discretion of the individual surgeon Since 1987, symptomatic immature pseudocysts have been managed by percutaneous drainage with catheter insertion under ultrasound guidance. A pigtail catheter greater than 8 Fr gauge in size was left *in situ* until drainage stopped; a sinogram was then performed through the catheter, before its removal, to exclude a persistent communication with the pancreatic duct[5]. From 1989, percutaneous drainage has been used routinely for all post-necrotic cysts (type I and type II) which were rapidly expanding or exceeding 10 cm in diameter. The average duration of follow-up was 12·3 months (range 1–76 months).

Results

Four patients in group I and one in group II, all treated conservatively, were lost to follow-up and excluded from subsequent study. The results in the remaining 78 patients were then analysed.

Amylase concentration in the pseudocyst fluid was measured in 66 per cent of patients and ranged from 18 000 to 1 440 000 units/l. CT scanning modified the interpretation of ultrasonographic findings in 18 per cent of patients concerning the location of the cyst, the presence of complications (infection or bleeding), or the presence of pancreatic necrosis. It also served as a guide to the optimal route for percutaneous drainage.

ERCP failed in five patients (three in group I and two in group II). The pancreatic duct was outlined in ten patients in group I and was normal with communication to the pseudocyst demonstrated in only one case of traumatic pancreatitis. ERCP in the 24 patients in group II revealed evidence of chronic pancreatitis (tortuous duct or calcification) in all cases. A communication between duct and pseudocyst was demonstrated in eight patients. One patient in whom ERCP failed showed communication between pseudocyst and duct on sinography following percutaneous drainage. There were no major ductal stricture in this group. ERCP was performed in 12 patients in group III and demonstrated stricture of the duct with cyst communication in all cases. Three patients had a 'chain of lakes' appearance.

Average size of pseudocyst and frequency of ductal communication are summarized in *Table 2*. Percutaneous drainage or surgical treatment was used in pseudocysts larger than 5 cm in diameter; all pseudocysts smaller than 4·7 cm resolved spontaneously.

Percutaneous drainage

Group I. In seven cases percutaneous drainage was used for rapidly expanding, immature cysts, and in five for pseudocysts of greater than 10 cm diameter. Drainage was performed within 10 days of the time of diagnosis. The average period of drainage was 18 days. No complications occurred and there were no recurrences at follow-up. Sinography through the catheter was performed in all cases and communication with the duct was never demonstrated.

Group II. In two patients with mature pseudocysts causing biliary obstruction, and in four patients with persistent large (>7 cm) painful pseudocysts, percutaneous drainage was undertaken approximately 2 weeks after diagnosis. Ductal communication was demonstrated in three patients in whom signs of chronic pancreatitis (calcification and tortuous duct) were present, but no ductal strictures were seen and there was free ductal flow. The communication closed spontaneously in 4–6 weeks. In two patients with prolonged drainage (28 and 47 days respectively), a fistula formed after the catheter entered the bowel. In the first case, removal of the catheter was uneventful and the pseudocyst did not recur. In the second case exploratory laparotomy was performed because of signs of systemic sepsis; this revealed a residual sterile fluid collection but no evidence of intestinal damage or leak. The collection was drained and the patient had an uneventful recovery. Sinography was performed in all cases and a pseudocyst–duct communication was demonstrated in three patients, although there was no evidence of ductal stricture.

Group III. No percutaneous drainage was used in this group.

Surgical treatment

Forty-one patients underwent surgery. Internal drainage procedures were performed in 28 patients, three patients in group I had surgical external drainage, three patients in group III had cyst-enterostomy plus ductal drainage; seven patients had pancreatic resection.

Complications

Overall, 17 patients experienced significant complications; these involved 11 patients in group I, five patients in group II and one in group III. Apart from those already mentioned in the percutaneous drainage group, these complications included pancreatic fistula (three), intra-abdominal abscess (four), haemorrhage (three), colonic necrosis (one), bowel leak from cyst-enterostomy (one), bowel obstruction (one), and several systemic complications such as renal and respiratory failure, coagulation disorders, etc.

Mortality

Four patients in group I and one in group II died. Two of the deaths occurred in patients managed conservatively and three followed surgical procedures (cyst-gastrostomy, two; distal pancreatectomy, one). The cause of death was intra-abdominal infection after operation in three patients and metabolic (total parenteral nutrition related) in one. In one case the cause of death remains unknown. This patient presented with jaundice (probably due to cholangitis) and renal failure and had an uncomplicated chronic 3 cm pseudocyst. He died suddenly 2 weeks after admission and autopsy was not performed.

Recurrence

The pseudocyst recurred in one patient in group II after percutaneous drainage. Three patients in group III had recurrence, two after cyst-gastrostomy and one after cyst-jejunostomy.

Table 2 *Average size of pseudocyst and frequency of cyst–duct communication*

Group	Number of patients	Average (range) cyst size (cm)	Cyst–duct communication
I	41	8 9 (2–25)	1*
II	25	4·6 (2–11)	9
III	12	7·1 (2–13)	12
Total	78	7 4 (2–25)	22

* Only 18 patients in group I were investigated by ERCP or sinogram

Discussion

Not all radiographic abnormalities which are reported as pancreatic pseudocysts are in fact pseudocysts Acute peripancreatic fluid collections commonly follow an acute attack of pancreatitis but lack a well-defined wall and in most instances rapidly resolve spontaneously. When associated pancreatic necrosis is suspected, percutaneous aspiration of the fluid collection for bacteriological sampling should be performed to exclude infected pancreatic necrosis. Without resolution the alternative is encapsulation and pseudocyst formation[6,7]. Central cavitary necrosis appears on CT scan as a well defined mass with a low density centre and convex margins; it results from pancreatic necrosis and an exudate of pancreatic fluid is present[8]. Percutaneous aspiration yields very scanty fluid. Conservative management is indicated provided fine needle aspiration excludes infection. If surgery is required, the most appropriate treatment is debridement and drainage

True pancreatic pseudocysts, on the other hand, are localized collections of pancreatic secretion, lacking an epithelial lining but possessing a clearly defined wall, made of fibrous tissue and adjacent viscera[9]. The classical approach to acute pseudocysts was to wait for 4–6 weeks before operating, in order to allow spontaneous resolution or maturation of the pseudocyst wall[1,10,11]. However, with the recent use of less invasive techniques, such as percutaneous aspiration or catheter drainage, this expectant policy may not be necessary as immature pseudocysts can also be drained without complications[5]. In the present study ten patients with pseudocysts of less than 2 weeks duration were drained percutaneously.

Could the suggested classification be used to tailor treatment to specific types of pseudocyst? Post-necrotic type I pseudocyst is readily cured by percutaneous drainage. This is ascribed to several factors including the absence of communication with the duct, the fact that the catheter is left *in situ* until drainage has stopped (thus preventing reaccumulation of fluid), and the use of sinography before removing the catheter. We believe that in the majority of these cases surgery is not necessary The surgical procedures performed in this group were decided by individual surgeons before the advent of percutaneous drainage and were associated with a significant morbidity and mortality. Others have demonstrated that even infected pseudocysts can be safely managed by percutaneous drainage[12]. It is our current policy to perform percutaneous drainage at a very early stage for all type I pseudocysts which are rapidly expanding and for large, symptomatic pseudocysts greater than 7 cm in diameter, which rarely resolve spontaneously. Smaller pseudocysts are monitored with serial ultrasound studies and percutaneous drainage is reserved for pseudocysts which increase in size or persist beyond 4 weeks. Routine use of ERCP in this group is not necessary as it would not modify management decisions.

Post-necrotic type II pseudocysts develop following acute attacks superimposed on chronic pancreatitis. In most instances the acute episode is obvious. Occasionally, however, acute signs are lacking and patients present with a clinical picture of chronic pancreatitis. In this situation, type II pseudocysts are diagnosed by ERCP which demonstrates signs of chronic pancreatitis without a dominant ductal stricture. In more than one-third of patients in this group, pseudocyst–duct communication was demonstrated While it has been postulated that recurrence after external drainage may be secondary to such communications[13], the present results show that percutaneous drainage may be effective (in three cases where communication was present). Prolonged drainage (5–6 weeks), however, led to erosion of the catheter into bowel in two cases. It is our view, therefore, that percutaneous drainage should be considered to have failed if drainage persists for longer than 6–7 weeks. Internal drainage was successful for type II pseudocysts in all instances and was associated with an acceptable morbidity rate.

Retention type III pseudocysts are uniformly associated with ductal strictures and pseudocyst–duct communication. Percutaneous drainage is not indicated[7], nor is surgical external drainage[14]. From the present study, however, it seems that internal drainage alone is also associated with a high recurrence rate. Andersson *et al.*[15] showed no difference in outcome after surgery for pseudocysts arising after acute pancreatitis compared with those complicating chronic pancreatitis. However, they did not state whether any of the patients with 'chronic' pseudocysts had ductal strictures. The present study demonstrates that outcome is not related to chronic pancreatitis itself, but to the condition of the pancreatic duct

A few anecdotal reports have highlighted the importance of ductal stricture in planning surgical management[16,17] Recently, Cremer *et al* [18] reported good results following endoscopic internal drainage (cyst-gastrostomy and cyst-duodenostomy) in 33 patients with pseudocysts associated with chronic pancreatitis. Of nine patients with ductal stricture, four (44 per cent) required pancreatico-jejunostomy at a later stage. Consequently these authors are currently stenting all strictured ducts.

The diagnosis of retention pseudocyst is based on the ERCP findings of obstruction and dilatation of the pancreatic duct It is essential, therefore, to perform ERCP in all patients with signs of chronic pancreatitis, as the findings could influence the subsequent management of the pseudocyst O'Connor *et al.*[19] found that ERCP modified tactics in approximately 50 per cent of patients. In the present study ERCP identified 12 retention pseudocysts The need to address the ductal pathology revealed by ERCP has been stressed by others[20,21]. Present results and those of others[22] show no increase in morbidity or mortality when a definitive procedure for chronic pancreatitis is performed at the time of surgery for the pseudocyst

The present study suffers from two potential pitfalls. First, not all patients in group I underwent ERCP, so the ductal anatomy is not known in all patients. However, 18 of 32 patients in whom the pseudocyst did not resolve spontaneously had ERCP or underwent sinography; in none of them was major ductal abnormality present and in only one patient was a pseudocyst–duct communication demonstrated. Second, it is frequently difficult to establish clinically whether patients presenting with their first attack of pancreatitis have chronic pancreatic changes While routine ERCP in all alcoholic patients could allow classification of these patients into groups I or II, the practical benefit of such investigation remains in doubt.

In conclusion, a classification of pancreatic pseudocysts is presented which may assist the clinician to select appropriate treatment. Type I pseudocysts can be adequately managed by percutaneous drainage alone. In type II pseudocyst pseudocyst–duct communication is often present and a prolonged period of percutaneous drainage may be needed. Surgical internal drainage is, however, adequate. Type III pseudocysts are associated with severe ductal pathology Percutaneous drainage is contraindicated and internal drainage carries a high recurrence rate. This implies a need to address the ductal pathology during the operation.

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Controlled trial of polyglycolic acid versus catgut and nylon for appendicectomy wound closure

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Six hundred and fifty patients undergoing appendicectomy were included in a prospective randomized controlled trial. At operation patients were allocated to control (chromic catgut ligatures and muscle closure, nylon skin closure) or study (polyglycolic acid ligatures and muscle and skin closure) groups. Wounds were examined by an independent observer daily in hospital and 1 month after operation. Wound infection was defined as discharge of serous or purulent material, or a grossly inflamed wound without discharging pus, or any evidence of intra-abdominal sepsis. Of the 650 patients (335 men, 315 women, age 5–80 years, median 18 years), 615 have completed follow-up. Groups were well matched for age, sex, degree of sepsis at operation, histological diagnosis and surgeon. Infection was significantly reduced in the study (polyglycolic acid) group (12·0 per cent) compared with the control (chromic catgut/nylon) group (21·2 per cent) ($\chi^2 = 9{\cdot}3$, $P = 0{\cdot}002$). Infection was significantly reduced in the polyglycolic acid group regardless of whether the appendix was inflamed or normal. These results indicate that suture material can influence the incidence of wound infection and that this is less frequent when polyglycolic acid sutures are used.

Wound infection continues to be an important cause of morbidity after surgery. Factors that worsen the risk of sepsis include operative trauma, necrotic tissue and bacterial contamination. Sutures and suturing techniques also play an important role in that overly tight ligatures increase tissue ischaemia and necrosis[1]. Also, use of the transcutaneous or subcuticular suturing technique is associated with a different rate of wound infection[2–4].

Sutures are foreign bodies and as such increase the risk of infection[1,5]. Elek and Conen observed, in studies with human volunteers, that an intradermal inoculum of 2×10^6 to $8{\cdot}5 \times 10^6$ staphylococci was necessary to produce lesions with pus formation, but if the organisms were introduced on a silk suture only 10^2 organisms were required to cause a stitch abscess[6]. Edlich *et al.* also showed that in contaminated tissues the presence of a suture significantly increased the incidence of infection, and suggested that sutures impair the ability of the wound to resist infection[7]. Furthermore, they showed that chemical composition, not physical configuration of the suture, was the most important determinant of early infection. In an animal study where absorbable sutures were implanted subdermally and the site was infected with *Staphylococcus aureus* (10^3–10^6 viable bacterial count), the incidence of infection associated with polyglycolic acid was significantly less than that associated with catgut, and was comparable to that of non-absorbable nylon sutures. The authors speculated that this lower incidence of sepsis might be a consequence of the reduced tissue reaction associated with polyglycolic acid or nylon compared with catgut, cotton or silk, or of an antibacterial action of the suture material itself.

In another animal study using synergistic bacterial contaminants, McGeehan *et al.*[8] also showed that chemical composition of sutures had a significant effect on the incidence of wound infection. In their study, sutures were implanted subdermally in guinea-pigs and the site was inoculated with a bacteria-rich suspension (*Escherichia coli* and *Bacteroides fragilis*) of 6×10^5 organisms. In the control group with no suture present, infection occurred in 27 per cent of animals and, as expected, wound infection was significantly greater with braided nylon (48 per cent) or catgut (55 per cent). However, the incidence of infection was lower with polyglycolic acid sutures (16 per cent) than in the control group. This reduction in the incidence of infection was not significant when compared with the control group (where no sutures were used) or with the Prolene® group, but it was significantly lower than in the braided nylon, catgut and silk groups These findings were confirmed in a subsequent study[9]

The present study was performed to determine whether the use of polyglycolic acid sutures could influence the incidence of wound infection in humans.

Patients and methods

All patients undergoing appendicectomy at Colchester General Hospital between February 1987 and November 1988 were included in a prospective randomized trial. Patients undergoing appendicectomy incidental to, or as part of, another procedure were excluded from the study. Patients received a single dose of metronidazole per rectum 1 h before surgery as prophylaxis against wound infection, and were randomized to control or study groups after opening the peritoneum by drawing a card from consecutively numbered sealed envelopes In the control group 1/0 chromic catgut (Softgut®, Davis and Geck, Gosport, UK) was used for all ligatures and sutures, and 3/0 monofilament nylon (Ethilon®, Ethicon Ltd , Edinburgh, UK) was used for subcuticular suture of the skin In the study group, 1/0 polyglycolic acid (Dexon®, Davis and Geck) was used for all ligatures and sutures, and 3/0 polyglycolic acid for subcuticular skin closure

The operative technique was similar for all surgeons Access to the abdomen was through a right iliac fossa muscle splitting (gridiron) incision A peritoneal culture swab was taken and evidence of the presence, or absence, of localized or generalized sepsis was noted. The appendix was removed and the stump was ligated but not buried with a purse-string suture. The wound was closed in layers by suturing the peritoneum, approximating the muscle layers and suturing the external oblique aponeurosis No wound spray or antiseptic was used Subcuticular skin closure was used throughout the study Drains were not used routinely The wound was dressed with a non-adherent absorbable dressing, which was removed on the first day after operation Subcuticular nylon sutures were removed on the seventh day after operation.

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Table 1 *Matching of control and study groups*

	Control group	Study group
Age		
≤10	33	44
11–20	141	148
21–30	71	59
31–40	18	29
41–50	25	15
51–60	7	4
61–70	9	5
71–80	3	4
Sex		
Male	162	154
Female	145	154
Antibiotic prophylaxis		
Protocol	272	283
Additional	28	19
Omitted	7	6
Operation site condition		
Generalized peritonitis	11	14
Localized pus	63	67
No pus	233	227
Histology		
Gangrenous	17	14
Inflamed	187	203
Normal	103	91

Differences between the two groups were not statistically significant

During hospital stay, wounds were examined daily for evidence of infection by an independent assessor throughout the study The same assessor checked all wounds for the duration of the study to avoid interobserver variation. All cases were followed up at 1 month. Patients not resident locally were contacted by post or telephone. All patients without complete follow-up were excluded from the study.

Wound infection was defined as a wound with *any* discharge of serous or purulent material, a grossly inflamed wound without discharging pus, or any evidence of intra-abdominal sepsis

Wound abscesses were treated by drainage alone whenever possible, and postoperative antibiotics were given only when clinically indicated for the treatment of major sepsis

Statistical analysis was performed with the aid of a Statgraphics statistical package, and the χ^2 test was used to analyse differences between the studied groups; a P value of $<0{\cdot}05$ was considered statistically significant

Results

Of 650 patients who entered the study, 615 completed follow-up There were 316 men and 299 women, aged 5–80 years (median 18 years). The groups were well matched for age, sex, weight and height of patients, surgeon performing the surgery, use of antibiotics, histological diagnosis and condition of the operative site (*Table 1*).

On histological examination, the appendix was reported to be gangrenous in 31 (5·0 per cent) cases, acutely inflamed in 390 (63·4 per cent) cases and normal in 194 (31·5 per cent) cases. A positive bacterial culture was obtained from the peritoneal swab in only 9·3 per cent of cases. The organisms grown from the culture swabs were mainly *E. coli* (47 per cent), *B. fragilis* (11 per cent), β-haemolytic streptococci (8 per cent) and skin flora (8 per cent).

There were no deaths. Major septic complications (intra-abdominal abscess) occurred in eight cases. Two of these required relaparotomy for drainage of the abscess. The remaining six cases were treated conservatively in hospital and the abscesses discharged spontaneously into the bowel. Major wound sepsis developed in six cases, which required exploration of the wound and drainage; five required antibiotic treatment.

The overall incidence of infection was 16·6 per cent. Infection was significantly more frequent when the appendix was gangrenous (45 per cent) than when it was inflamed (15·4 per cent) ($\chi^2=17{\cdot}7$, $P<0{\cdot}001$). The incidence of infection in cases with histologically normal appendices was 14·4 per cent.

Most wound infections occurred after patients had been discharged from hospital. Only 18·5 per cent of complications occurred during the first 6 days after surgery and 73·2 per cent occurred between days 7 and 10 after operation. The mean hospital stay was 5 days and it was therefore not possible in most cases to obtain culture swabs from patients with postoperative infection.

Infection occurred in 102 (16·6 per cent) of the 615 patients who completed follow-up; 65 were in the control group (21·2 per cent of the group) and 37 were in the study group (12·0 per cent of the group) ($\chi^2=9{\cdot}3$, $P=0{\cdot}002$) (*Table 2*). In patients with inflamed appendices, wound infection occurred in 36 of 187 (19·3 per cent) of the control group and 24 of 203 (11·8 per cent) of the study group ($\chi^2=4{\cdot}1$, $P=0{\cdot}042$). More surprisingly, a similar significant difference occurred in patients with histologically normal appendices. Wound infection occurred in 20 of 103 (19 per cent) of the control group but in only eight of 91 (9 per cent) of the study group ($\chi^2=4{\cdot}4$, $P=0{\cdot}035$). In the 31 cases of gangrenous appendicitis, the incidence of infection was higher, occurring in nine of 17 (53 per cent) of the control group and five of 14 (36 per cent) of the study group. This difference was not significant (Fisher's exact two-tailed test, $P=0{\cdot}47$).

Analysis of the 49 cases with positive peritoneal swabs showed a smaller but not significantly different proportion of postoperative infection in the polyglycolic acid group (29·1 per cent) compared with the control group (53·8 per cent, $\chi^2=1{\cdot}06$, $P=0{\cdot}30$). The incidence of intra-abdominal abscess and the use of additional antibiotics for major wound sepsis was not significantly different between control and study groups.

Discussion

Wound infection continues to be a problem in surgery despite advances in surgical technique, antibiotic prophylaxis and wound care. The results of prevention of wound infection after appendicectomy have been extensively reviewed by Krukowski *et al.*[10]. Other studies have examined the role that suture techniques play in the incidence of wound infection[2–4].

It is known from animal studies that wound infection occurred significantly less frequently in wounds where polyglycolic acid was used[6–8], but similar studies have never been done in humans. Clinical studies that have used absorbable sutures have compared surgical technique rather than the role of the suture material itself[2] or have not been randomized or adequately controlled[11,12]

One study that used a similar suturing technique closed periodontal flaps with either interrupted silk or polyglycolic

Table 2 *Incidence of infection in the study (polyglycolic acid) and control (catgut/nylon) groups*

	Control group	Study group	χ^2	P value
Overall infection				
No infection	242	271		
Infection	65 (21·2)	37 (12·0)	9·3	0·002
Inflamed appendicitis				
No infection	151	179		
Infection	36 (19·3)	24 (11·8)	4·1	0·042
Gangrenous histology				
No infection	8	9		
Infection	9 (53)	5 (36)		0·47*
Normal histology				
No infection	83	83		
Infection	20 (19)	8 (9)	4·4	0·035

Values in parentheses are percentages. * Fisher's exact two-tailed test acid sutures, which were removed 4–5 days after operation. No clinical difference in tissue reaction between suture materials was observed, but experimental data showed that there was a significant reduction in bacterial transmission (migration of bacteria down the suture tract) with polyglycolic acid when compared with silk[13].

Subcuticular closure was chosen in this trial as this technique relates closely to the animal studies on which the study was based[8] and to minimize difficulties in wound assessment as only two skin puncture sites had to be assessed together with the skin edges of the wound itself. The fact that the appendix stump was not buried after ligation should not have influenced the incidence of complications[14,15].

The incidence of infection in the present study (16·6 per cent) was comparable to that of other series[10] but was higher than anticipated. Infection was related to the degree of sepsis at operation (*Table 1*) It was a particular surprise that the incidence of wound infection was 19 per cent in uninflamed appendices using the conventional suture materials that we had used for many years We believe that this was due in part to the strict criteria used for defining infection. It remains possible that some of the wounds discharged only serous fluid rather than pus or infected fluid, but they still represent a wound that has failed to heal primarily. Earlier postoperative assessment, say at 10 days, would have allowed us to assess the infected wound more closely, but clinically this is too short a follow-up. To recall patients twice is not practical and a high compliance would not have been achieved.

The results of this prospective clinical study are similar to the results obtained in the animal models used to compare sutures[8,9]. Overall, infections were more frequent in controls compared with the polyglycolic acid group (21·2 per cent *versus* 12·0 per cent, $\chi^2=9{\cdot}3$, $P=0{\cdot}002$). Significant differences were seen regardless of whether the appendix was inflamed (19·3 per cent *versus* 11·8 per cent, $\chi^2=4{\cdot}1$, $P=0{\cdot}042$) or normal (19 per cent *versus* 9 per cent, $\chi^2=4{\cdot}4$, $P=0{\cdot}035$).

Explanation of these findings can only be tentative, but it seems likely that polyglycolic acid does have some properties that reduce infection. Adherence of bacteria to braided polyglycolic acid sutures is significantly less than to braided nylon[16,17], and infectivity of contaminated polyglycolic acid sutures is lower than that of other braided sutures such as nylon or silk[17]. No data on bacterial adherence to monofilament polyglycolic acid has been published as this suture is not manufactured.

Polyglycolic acid sutures are reabsorbed by a process of hydrolysis. The degradation product, glycolic acid, has an intrinsic antibacterial action and has been shown to reduce staphylococcal bacterial counts *in vitro* in an acidic environment[7] This action is minimized when the solutions are buffered. Nevertheless, it is possible that bacterial growth is reduced by the products released during the reabsorption of the suture material, thus reducing the infective inoculum. This effect may be enhanced initially when the wound is ischaemic and therefore acidic.

Glycolic acid also enhances leucocyte function as it increases the respiratory burst activity as measured by an increase of intracellular hydrogen peroxide production[18] Finally, the finding that polyglycolic acid causes significantly less tissue reaction[7,17,19] may be sufficient to explain the reduction in wound infection.

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Randomized trial of intra-arterial recombinant tissue plasminogen activator, intravenous recombinant tissue plasminogen activator and intra-arterial streptokinase in peripheral arterial thrombolysis

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Sixty patients were recruited into a randomized parallel group comparison of three thrombolytic regimens for acute or subacute peripheral arterial thrombosis. There were no significant differences in age, duration of history, length of occlusion or presence of neurosensory deficit between the groups. Initially successful lysis was significantly greater with intra-arterial (IA) recombinant tissue plasminogen activator (rt-PA) than with either streptokinase (Sk) ($P<0{\cdot}04$) *or intravenous (IV) rt-PA* ($P<0{\cdot}01$)*. The duration of therapy varied from a median of 35 h with IA rt-PA to 40 h with Sk* ($P>0{\cdot}5$)*. The median (confidence interval) increase in ankle:brachial pressure index following IA rt-PA of 0·57 (0·33–0·82) was significantly higher than for either Sk of 0·24 (0–0·57) or for IV rt-PA of 0·18 (0–0·41). Limb salvage at 30 days was achieved in 80, 60 and 45 per cent respectively for IA rt-PA, Sk and IV rt-PA. Haemorrhagic complications occurred in six patients following Sk and in 13 following IV rt-PA; only one minor haemorrhage occurred following a catheter perforation in a patient who received IA rt-PA* ($P<0{\cdot}05$)*. IA rt-PA provides a more effective, safer fibrinolytic regimen than conventional therapy with Sk. IV rt-PA has not been as successful and carries a significantly higher risk of haemorrhagic complications.*

Thrombolytic agents have been shown to have the potential to limit skeletal muscle damage after acute ischaemia[1]. This phenomenon is probably due to improved patency of the distal vessels, and in particular the microvasculature, allowing watershed areas to survive. Furthermore, it has been demonstrated that balloon catheter thromboembolectomy is unable to achieve complete removal of distally propagated thrombus[2–4]. Continued attempts to remove residual thrombus can result in de-endothelialization of the artery and injury to the vessel wall[5,6]. Inflamed endothelium has also been shown to have increased procoagulant activity[7] and arterial ischaemia impairs local endogenous fibrinolysis[8]. This is evidence supporting either a primary or an adjunctive[9–11] role for peripheral arterial thrombolysis in the management of acute arterial ischaemia.

Following experience with intra-arterial (IA) recombinant tissue plasminogen activator (rt-PA) in an open study[12], the next logical stage was to compare rt-PA directly with streptokinase (Sk) in a randomized trial to allow a valid comparison of the clinical efficacy of the two agents. A third arm of the randomization procedure included intravenous (IV) rt-PA at a variable rate of infusion but with a fixed total dose. Theoretically, rt-PA is only activated by fibrin-bound thrombus[13] and so should be equally as active when given systemically by the intravenous route as it is when given locally via an artery.

In the following study Sk was given at a standard dosage of 5000 units/h as used by most investigators[14–17], with the concurrent administration of IA low-dose heparin 250 units/h. The dose of IA rt-PA used[12] was 0·5 mg/h, which is considerably less than the dose used by Graor *et al.*[18]; previous experience in this department with higher doses revealed a higher incidence of haemorrhagic complications without any obvious increase in lysis rate[19].

Systemic administration of rt-PA has been shown to be of value in coronary thrombolysis[20–22]. However, in peripheral arterial thrombosis the length of the occlusion, the diameter of the vessel and the duration of history are all considerably greater than in coronary thrombosis. Hence a rapid onset, short duration, profound thrombolytic state is unlikely to achieve the same success if applied to peripheral arterial thrombosis. If systemic thrombolysis is to work for peripheral arterial thrombosis, a *fibrin-specific* agent must be given over several hours without incurring a profound systemic lytic effect; rt-PA has this potential and the randomization procedure was designed to allow comparison of its systemic efficacy with that of locally administered Sk and rt-PA. Successful systemic administration would remove the need for a skilled interventional radiologist to position an IA catheter, although residual stenosis would still require dilatation at a later date.

This study is the first randomized comparison of IA Sk and IA rt-PA, it is also the first assessment of the efficacy and safety of IV rt-PA for peripheral arterial thrombolysis.

Patients and methods

Patients

Sixty patients were entered into the study, 20 into each limb of the trial. All patients gave a history of a sudden onset or deterioration of their peripheral limb ischaemia of less than 30 days duration sufficient to cause critical ischaemia[23]. Patients with ischaemia severe enough to cause neurosensory deficit were offered surgical reconstruction, if

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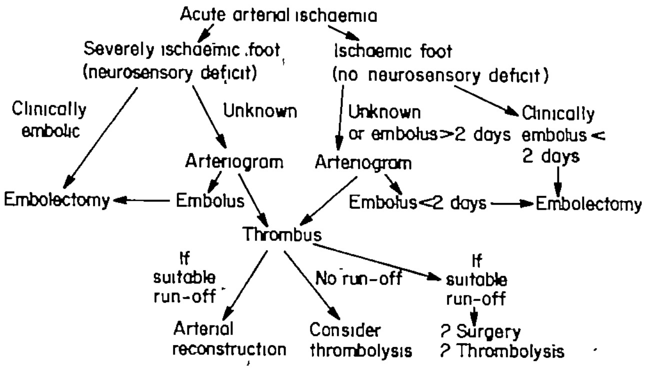


Figure 1 *The Nottingham management protocol for acute peripheral arterial ischaemia*

Table 1 *Exclusion criteria from thrombolysis*

1. Childbearing potential
2. Recent major trauma or surgery (<10 days)
3. Known bleeding diathesis
4. Added risk of bleeding, e.g. active peptic ulcer
5. Cerebrovascular accident within the previous 2 months
6. Unable or unwilling to give fully informed consent
7. Proximal arterial emboli of <2 days duration
8. Arterial thrombosis causing severe ischaemia with good run-off

feasible, at the referring hospital. Similarly, those with a clinically obvious embolic source and those proven to have proximal emboli of less than 2 days duration were managed by standard balloon catheter embolectomy and were not considered for the trial (*Figure 1*) With the exclusions detailed in *Table 1*, all other patients were considered eligible for thrombolysis and, if informed consent was obtained, were randomized according to *Figure 2*.

Following randomization, all lesions were confirmed by angiography. If the patient was due to receive IV rt-PA, an IV digital subtraction angiogram (DSA) was performed to avoid an arterial puncture before systemic administration of a lytic agent, albeit a fibrin-specific agent. For all other patients a transfemoral Seldinger type angiogram was performed. For iliac, common femoral and flush occlusions of the superficial femoral artery, the catheter was inserted via the opposite groin. For more distal lesions an antegrade approach was used to reduce the length of IA catheter and in particular to allow a more accurate technique of withdrawing the catheter at stages on the ward. A 4 or 5 Fr gauge catheter was used, of a straight (antegrade) or sidewinder (contralateral) type.

After the catheter had been inserted, or after DSA for those due to receive IV rt-PA, patients were returned to a side room of the ward where strict bed rest was enforced to reduce movement at the catheter entry site to a minimum. Measurements of blood pressure, pulse and temperature were performed on an hourly basis by the nursing staff, and radiographs were performed twice daily by the medical staff. In addition to the normal clinical assessment, particular note was made of the presence or absence of neurosensory deficit, the quality of capillary perfusion, the Doppler ankle arterial pressures, and the ankle:brachial pressure index (ABPI) at each assessment period. If the patient deteriorated during treatment, clinical and radiographical assessments were made to determine if any surgical intervention might be of benefit and whether further lytic therapy was justified. For those receiving IA therapy, repeat angiograms were performed after 4 h and then at intervals of 12 h throughout the infusion period. For iliac lesions 15–20 ml, and for femoral, popliteal or tibial lesions 10–15 ml iopamidol (Niopam 300, E. Merck Ltd, Alton, Hampshire, UK) were injected rapidly into the IA catheter and a single film angiogram of the lesion obtained. To enhance the quality of the pictures, the contrast was used undiluted with the infusion temporarily switched off, and a rapid bolus was given with immediate exposure. A similar technique was used to monitor withdrawal of the catheter, obviating the need to return to the radiology department.

The angiogram was used to determine: (1) if lysis was proceeding, (2) if the catheter was still in the optimal position for effective lysis (i e. inserted directly into the occluding thrombosis), and (3) if there were any residual significant stenoses that required angioplasty before removal of the catheter. For patients receiving systemic lysis, a repeat IV DSA was performed after the total dose was administered or after significant clinical improvement had occurred.

Methods

Before beginning therapy, all patients were examined clinically, particular attention being paid to the presence or absence of neurosensory deficit, ankle artery pressure, ABPI and electrocardiograph and echocardiogram findings.

Laboratory monitoring. In addition to a haemoglobin estimation, white cell count, platelet count, full clotting screen, and urea and electrolyte estimation, all patients had serum saved for blood grouping. At the beginning of therapy, every 12 h during therapy, and at 12 h after therapy, venous blood was obtained for the above tests and for the determination of fibrinolytic profiles.

Infusion protocols Sk (Streptase, Hoescht, Hounslow, UK) was infused IA at 5000 units/h with 250 units/h sodium heparin (Unihep Leo 1000, Leo Laboratories, Bucks, UK). rt-PA (Boehringer Ingelheim, Bracknell, UK) was infused IA at 0·5 mg/h with 250 units/h sodium heparin. For patients receiving systemic lytic therapy with rt-PA, all were able to receive a maximum total dose of 100 mg rt-PA. Four rates of infusion (five patients each) were used: 1, 2, 5 and 10 mg/h

Therapy was continued until complete lysis was achieved, or the patient deteriorated, or no further discernible lysis occurred either clinically or radiographically after a 12 h period.

Post-lysis management. Following completion of lysis, with or without angioplasty, the catheter was withdrawn and heparin therapy was commenced IV after haemostasis had been achieved in the groin The initial rate was 1000 units/h and, following a check on the full clotting screen after 12 h, it was then increased to achieve an activated partial thromboplastin time (APTT) of approximately 2–3 times the control value. The only proviso was that if the thrombin clotting time (TCT) at this stage was still in excess of 60 s, despite a normal APTT, the heparin infusion was left at 1000 units/h for a further 12 h. This was an attempt to reduce the post-lysis haemorrhagic complications associated with excessive heparin therapy in the presence of deranged clotting, secondary to the effects of the lytic agent itself and to the products of lysis. Warfarin was normally commenced 48 h after lysis, with systemic heparinization continued until the International Normalized Ratio (INR) was stable at between 2 and 3. Patients with any contraindication to warfarin were treated with aspirin alone (75 mg/day).

Following discharge, follow-up was performed at 30 days and 3 months after the end of lysis. If the patient became symptomatic again, or if the ABPI diminished by ≥0·2, an IVDSA was performed to assess patency and to detect significant stenoses amenable to angioplasty.

All patients gave fully informed consent The trial was approved by the Medical Ethical Committee of the University Hospital, Nottingham. Randomization was performed using a random number program on a Casio FX-361 calculator using preassigned 'last digits' for each group All statistical analyses were performed using the χ^2, Mann–Whitney *U*, or Student's *t* test as appropriate, and unless otherwise stated, numbers refer to median values All statistical calculations were performed on an ICL3900 mainframe computer using the MINITAB (Minitab Corporation, USA) program

Results

A total of 60 patients were recruited from many different centres over a 15 month period from January 1988 until March 1989. Six patients were excluded, two of the six due to technical

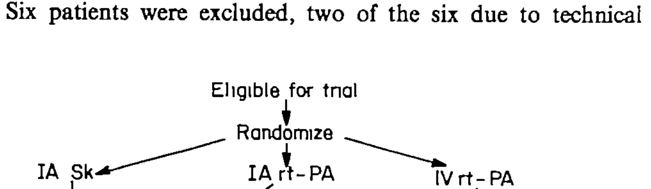

Eligible for trial
Randomize
IA Sk
IA rt-PA
IV rt-PA
Seldinger transfemoral arteriography
Digital subtraction angiography (IV)
5000 units/h Sk +250 units heparin
0 5 mg/h rt-PA + 250 units heparin
Variable dose 1-10 mg/h rt-PA (max dose 100 mg)

Figure 2 *Randomization protocol Sk, Streptokinase, rt-PA, recombinant tissue plasminogen activator; IV, intravenous, IA, intra-arterial*

Table 2 *Patient details*

	IA Sk ($n=20$)	IA rt-PA ($n=20$)	IV rt-PA ($n=20$)
Age (years)	70(15)	70(10)	72(11)
Weight (kg)	68(18)	72(16)	67(10)
Previous cerebrovascular accident	4	1	3
Previous myocardial infarction	5	5	2
Angina/congestive cardiac failure	3	2	3
Diabetic	6	3	2
Smokers	11	14	10

Values for age and weight are mean(s.d.); Sk, streptokinase; rt-PA, recombinant tissue plasminogen activator; IA, intra-arterial, IV, intravenous, no significant differences, χ^2 test

Table 3 *Clinical details*

	IA Sk ($n=20$)	IA rt-PA ($n=20$)	IV rt-PA ($n=20$)
Duration of history (days)	16(10)	14(9)	12(11)
Length of occlusion (cm)	19(15)	21(14)	18(14)
No. with occlusion >25 cm	6	9	5
ABPI before therapy	0·10(0·18)	0·13(0·17)	0·14(0·19)
Median(range) ABPI before therapy	0(0–0·51)	0(0–0·49)	0(0–0·64)
Ankle pressure zero (n)	13	13	11
Neurosensory deficit (n)	10	13	8

Values are mean(s.d.) unless otherwise stated; Sk, streptokinase; rt-PA, recombinant tissue plasminogen activator; IA, intra-arterial, IV, intravenous; ABPI, ankle/brachial pressure index

difficulty making it impossible to position the IA catheter correctly within the lesion. Both of these patients underwent surgical reconstruction, an *in situ* saphenous vein femoral–tibial bypass in one and a Dacron® (E.I. du Pont de Nemours and Co., UK) femoro–femoral bypass in the other, which achieved limb salvage with patent grafts at 3 months. A further two patients had established motor paralysis, paraesthesia and blistering; primary amputation was considered to be the correct management. One patient was moribund with severe cardiac failure and died within hours of admission, and the final patient had extensive venous and arterial thrombosis of the leg, probably secondary to bronchial carcinoma, and died following an above-knee amputation.

Twenty patients were entered into each of the three treatment arms. The mean(s.d.) age overall was 71(12) years with a mean(s.d.) body-weight of 69(15) kg. There were 39 men and 21 women distributed evenly throughout the three groups. There was no significant difference between the three groups in terms of age, body-weight, smoking habit, pre-existing medical conditions, duration of history, length of occlusion or severity of ischaemia (*Tables 2* and *3*). Eight patients were known to have had a documented cerebrovascular accident outside the exclusion criteria of 2 months. At least half of the patients in each group admitted to being smokers at the time of the acute peripheral ischaemic event. All three treatment groups were well matched in terms of the type, aetiology and proximal extent of the lesion (*Tables 4* and *5*).

The mean duration of history varied from a mean(s.d.) of 12(11) days in the IV rt-PA group to 16(10) days in the Sk group (no significant differences between any groups, Mann–Whitney *U* test). Similarly the three groups were well matched in terms of the length of occlusion with a mean value between 18 and 21 cm for all three groups, and a substantial number in excess of 25 cm (*Table 3*) (no significant differences, Mann–Whitney *U* test). The site of the lesion did not present a particular difficulty as lesions from the origin of the common iliac to the distal popliteal and tibial vessels proved amenable to thrombolytic therapy.

Clinical and radiological results

Although all three treatment regimens worked, there were substantial differences between them in terms of efficacy, reliability and safety. As the systemically treated group all had the same, fixed maximum total dose, they will be compared as a whole group. The longest occlusion treated successfully with lysis varied from 17 cm in the IV rt-PA group to 50 cm in the Sk and 60 cm in the IA rt-PA group. Radiological confirmation of lysis was seen in 16 (80 per cent) following Sk, but in only nine (45 per cent) of those receiving IV rt-PA of whom three achieved only partial lysis (defined as lysis of the lesion down to the next major artery distally). In contrast, all patients in the IA rt-PA group exhibited significant lysis ($P<0·04$) (*Table 6*). This difference in effectiveness of lysis is reflected in the ability to perform an angioplasty of visible residual stenoses (*Figures 3* and *4*), and in the clinical improvement obtained. The median duration of lysis was not significantly different between Sk and IA rt-PA, 40 h (range 14–64) and 35 h (range 14–64) respectively. The median overall increase in ABPI following lytic therapy was 0·57 (range 0·33–0·82) in the IA rt-PA group, significantly higher than in either of the other treatment groups ($P<0·001$, Mann–Whitney *U* test).

The three end-points of paramount importance are those of limb salvage, amputation and death. These have been evaluated at 30 days and 3 months after presentation (*Table 7*). Asymptomatic limb salvage at 30 days was achieved in 16 patients receiving IA rt-PA, compared with 12 after IA Sk therapy. While this difference is not statistically significant, the 95 per cent confidence limits confirm a trend in favour of IA rt-PA therapy (−8 per cent to 48 per cent). Furthermore, the amputation rate at 30 days was significantly less with IA rt-PA

Table 4 *Types of occlusion*

	Sk ($n=20$)	IA rt-PA ($n=20$)	IV rt-PA ($n=20$)
Thrombosis	16	17	16
Embolus	4	2	2
Post-procedure	0	1	2

Table 5 *Sites of occlusion*

Proximal limit of occlusion	Sk ($n=20$)	IA rt-PA ($n=20$)	IV rt-PA ($n=20$)
Common iliac/external iliac	5	5	6
Femoral	11	12	7
Popliteal	3	3	5
Tibial	1	0	2

Table 6 *Results of thrombolysis*

	IA Sk ($n=20$)	IA rt-PA ($n=20$)	IV rt-PA ($n=20$)
Radiological success			
complete	16	17	6
partial	0	3	3
total (%)	80	100*	45
Radiological failure	4	0	11
Angioplasty	4	8	1
Clinical improvement (%)	16 (80)	20 (100)	11 (55)
Median increase in ABPI (ranges)	0·24 (0–0·57)	0·57** (0·33–0·82)	0·18 (0–0·41)

* $0·01<P<0·04$, ** $P<0·001$ compared with other two groups

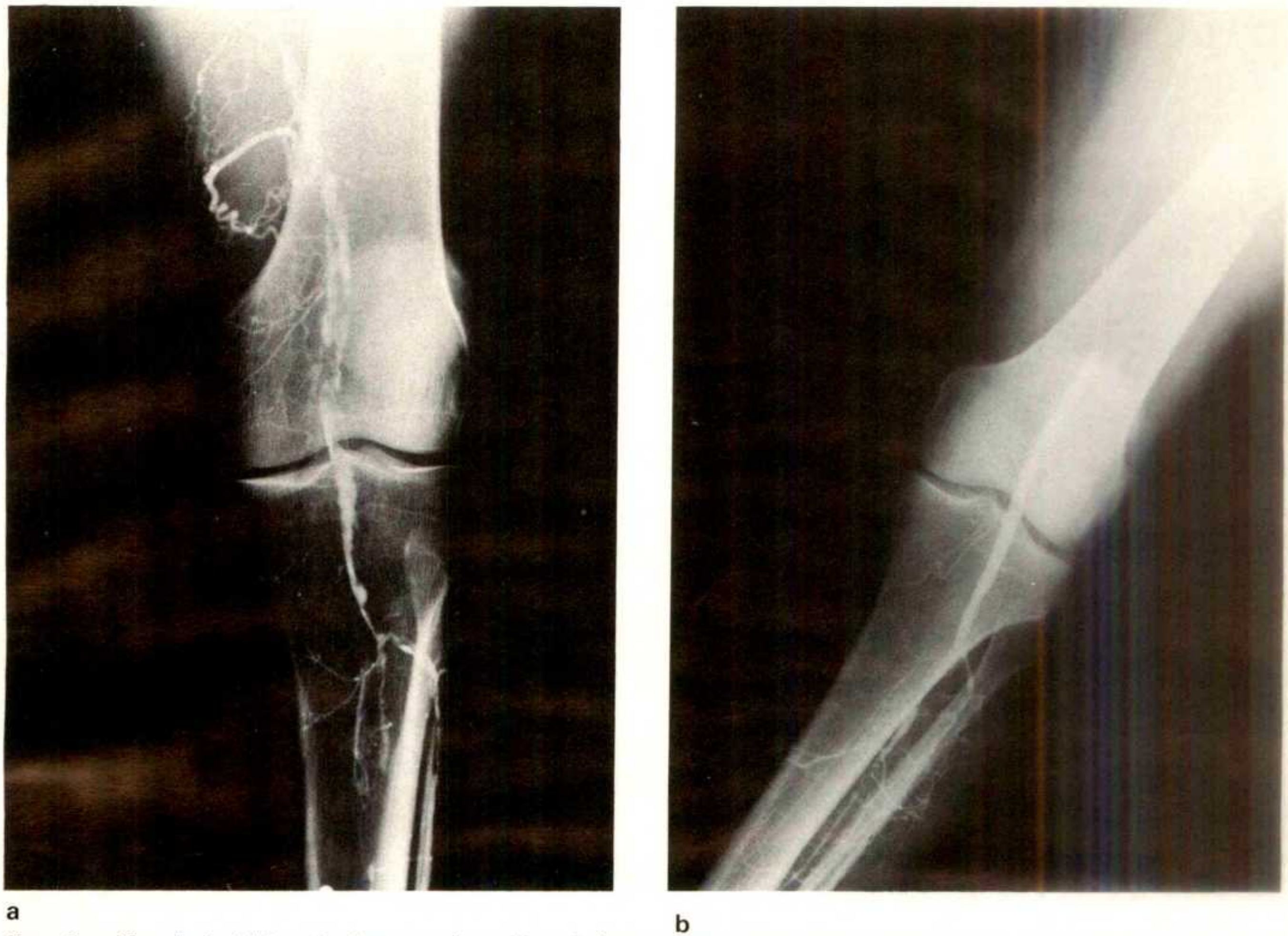


Figure 3 **a** *Thrombosis of left popliteal artery and run-off vessels;* **b** *intra-arterial rt-PA restores patency to allow angioplasty (shown here) of a residual stenosis*

than with Sk ($P < 0.05$, Mann–Whitney *U* test). In contrast, however, are the disappointing results obtained with systemic administration of rt-PA (*Table 7*). Although 14 patients in this group had their limbs intact at 30 days, five were still critically ischaemic. Furthermore, three patients required surgical reconstruction or IA thrombolysis following failure of the systemic regimen.

After 3 months ten limbs were salvaged in the IV rt-PA group, compared with 12 in the IA Sk group and 15 in the IA rt-PA group. There was no significant difference in limb salvage, amputation or death rates between the IV rt-PA subgroups. In general, those patients achieving complete lysis with 30-day limb salvage continued to have a patent vessel and an asymptomatic limb at 3 months. In the patients achieving lysis with patency at 30 days, there was no difference in the initial length of occlusion between the three groups. The median (interquartile range) lengths were 9 (5–26), 16 (11–35) and 15 (5–21) for the Sk, IA rt-PA and IV rt-PA groups respectively.

By adhering to the NIH conference guidelines[24] and in particular to the exclusion criteria of this trial, complications were fortunately few in number and of limited severity (*Table 8*). Locally administered rt-PA was undoubtedly safest; no cerebrovascular accident, major or minor haemorrhage could be attributed to this agent. No period of hypotension occurred at any time during the infusion or during subsequent treatment with heparin, and no fresh frozen plasma or platelet infusion was required (*Table 8*). One popliteal perforation did occur in this group, probably secondary to an inadvertent puncture of the vessel wall with the guidewire at the time of diagnostic angiography and insertion of catheter, and was associated with a calf haematoma. Patency of the popliteal and superficial femoral vessels in this patient were still achieved at 30 days, confirmed by IVDSA. This accident could not be ascribed to the drug. The IA rt-PA group also contained the only significant case of distal embolization during the procedure. The infusion was continued with rapid resolution and patency of the entire segment containing the lesion. Rethrombosis remained a problem with both agents, although it was twice as common in the Sk goup as in the IA rt-PA group (*Table 8*).

In the Sk group three patients required blood transfusion for major haemorrhage causing hypotension, and a further three patients experienced less severe haemorrhage not requiring specific correction but resulting in a substantial haematoma, usually at the catheter entry site. Haemorrhage was frequently associated with the use of IV rt-PA, but fortunately it was mostly minor in the sense that hypotension did not occur and transfusion was deemed unnecessary. Nevertheless, oozing from venepuncture sites often required the application of pressure dressings to secure haemostasis. One patient experienced a cerebrovascular accident while receiving IV rt-PA (5 mg/h for 4 h). The diagnosis was confirmed by computed tomography, with good resolution of symptoms by 7 days. The haemorrhage fortunately occurred at the site of an old infarct and so there was comparatively little deficit (left seventh nerve palsy and left upper monoparesis), with rapid resolution (*Figure 5*). A repeat scan was performed after 1 month and revealed a further asymptomatic haemorrhage in the opposite hemisphere (*Figure 6*). The patient was not taking any antiplatelet, anticoagulant or fibrinolytic medication at the time.

Discussion

This study was designed to provide the first randomized comparison of rt-PA and Sk in the field of peripheral arterial

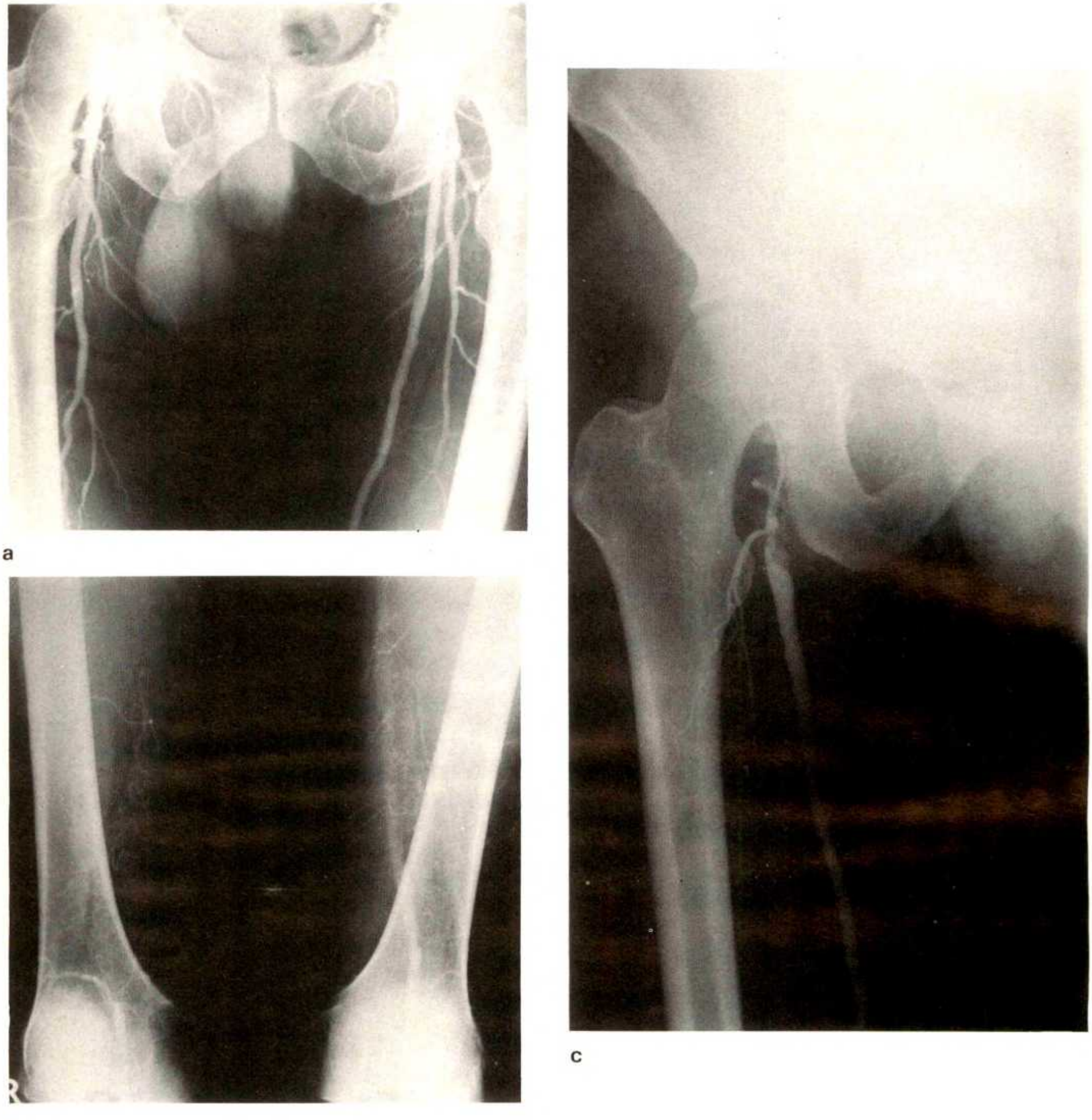
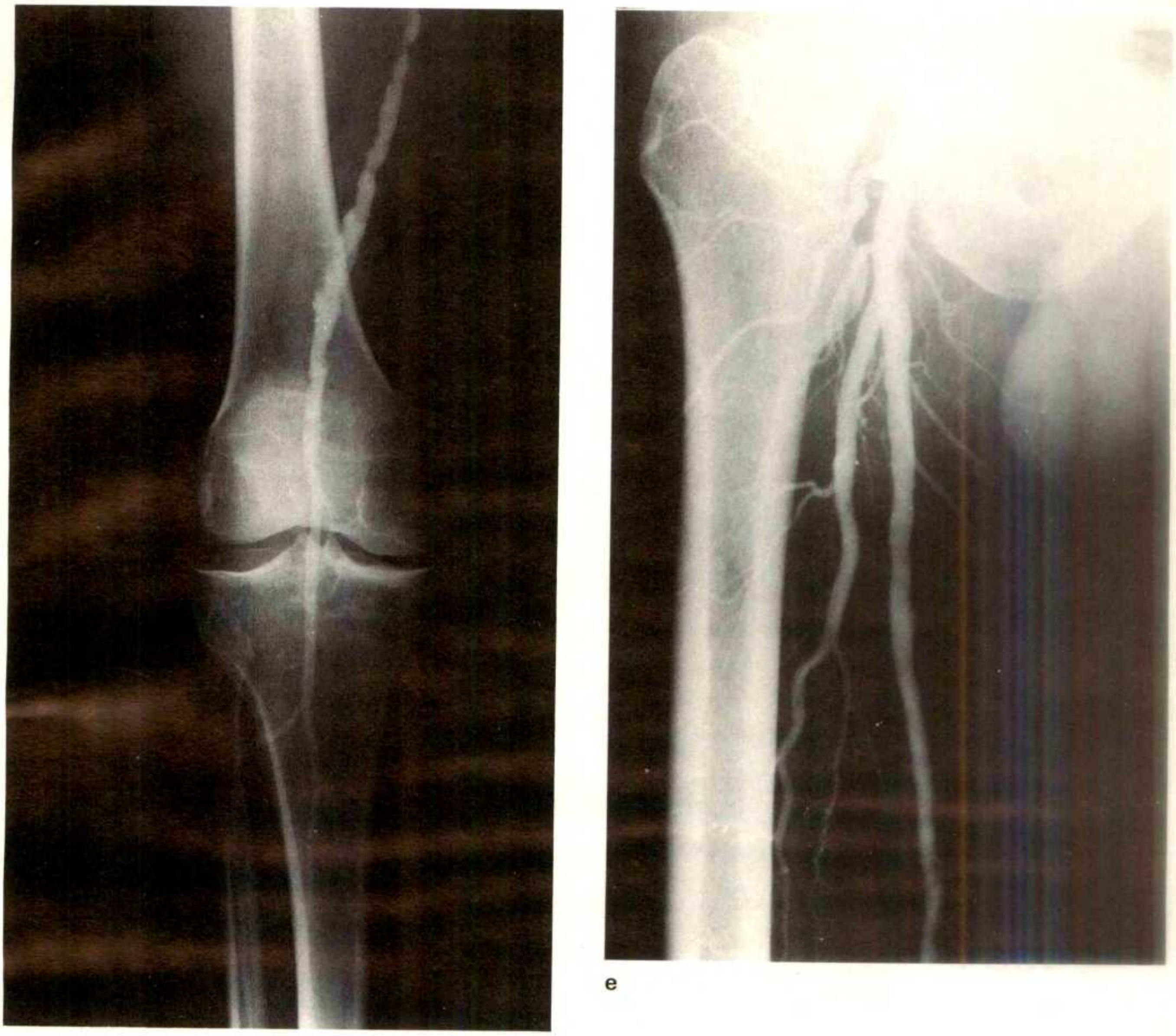


Figure 4 **a** *Flush thrombotic occlusion of right superficial femoral artery with* **b** *reconstitution of popliteal via collaterals. Clearance of the thrombus with IA rt-PA reveals significant stenoses in the* **c** *proximal and* **d** *distal superficial femoral artery. Stenoses were successfully angioplastied;* **e** *shows proximal result*

thrombolysis; it was hoped that it might determine whether or not the theoretical advantage of increased lytic potential and 'fibrin-specificity' of rt-PA might translate into a clinically useful increase in limb salvage, reduction in mortality rate and reduction in haemorrhagic complications. Local IA rt-PA offered a 20 per cent increase in limb salvage (80 per cent) at 30 days over conventional therapy with IA Sk. Although this did not achieve statistical significance there was a strong bias in favour of IA rt-PA. Comparison with other regimens in different centres is often difficult because of large study population differences, especially owing to the inclusion of a variety of indications such as thrombosed arteriovenous fistula which has a totally different prognosis from that of lower limb thromboembolism[14,25]. Using high-dose urokinase, McNamara and Fischer[26] demonstrated an 83 per cent lysis rate in association with a 4 per cent incidence of major haemorrhage; this is little better than our results with low-dose Sk, despite the urokinase being used in a younger population (mean age 59 years) in whom 72 of 83 lesions were less than 10 days old. Furthermore, ten patients had thrombosed arteriovenous dialysis shunts, but insufficient data were provided to allow separation of this good prognosis group from those with lower limb thromboembolism. Using Sk, Graor *et al.*[14] achieved an initial patency rate of 55 per cent in thrombosed peripheral lower limb arteries. This same group (Risius *et al.*[27]) later published much improved results with rt-PA with complete thrombolysis occurring in 20 out of 21 patients. Unfortunately no data were given about the mean or median age of the patients, or of the duration of history. Nevertheless, results from the present study show an equally



d

e

Table 7 *Outcome at 30 days and 3 months after thrombolysis*

	IA Sk ($n=20$)	IA rt-PA ($n=20$)	IV rt-PA ($n=20$)
30-day limb salvage:			
Asymptomatic	12 (60)	16 (80)	9 (45)
Critical ischaemia	0	0	5
Amputation	6 GSA, 1 BKA	1 GSA	0
Death	1 pneumonia	1 pneumonia 2 MI	2 pneumonia 1 MI
Reconstructed	0	0	2
IA lysis	0	0	1
3-month limb salvage:			
Asymptomatic	12 (60)	15 (75)	10 (50)
Critical ischaemia	0	0	1
Patency	11	14	7
Amputation	6	1	1
Death	2	4	5
Reconstructed	0	0	2
IA lysis	0	0	1

Values in parentheses are percentages; GSA, Gritti–Stokes amputation; BKA, below-knee amputation

Table 8 *Complications of thrombolysis*

	IA Sk ($n=20$)	IA rt-PA ($n=20$)	IV rt-PA ($n=20$)
Cerebrovascular accident	0	0	1
Haemorrhage			
Major	3	0	3
Minor	3	0	9
Perforation	0	1	0
Rethrombosis	4	2	0
Embolization	0	1	0

Sk, streptokinase; rt-PA, recombinant tissue plasminogen activator; IA, intra-arterial; IV, intravenous

favourable response using rt-PA at a much lower dose. Encouraging results have also been reported by Verstraete *et al.*[28] using comparatively high doses of rt-PA, with an initial patency of up to 94 per cent, but with a 37 per cent incidence of haemorrhagic complications. Lower doses, such as those used in the present study, appear to offer similar thrombolytic success at lower complication rates.

In the present study there were significant advantages of IA

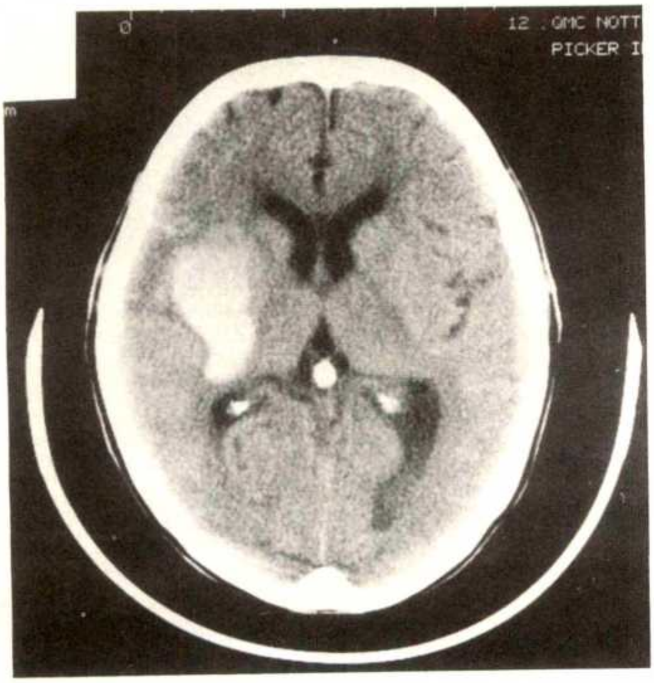


Figure 5 *Computed tomogram after contrast agent injection following acute onset of a left upper monoparesis in a patient who had received IV rt-PA. A large right temporoparietal haemorrhage is seen at the site of a previous cerebrovascular infarct*

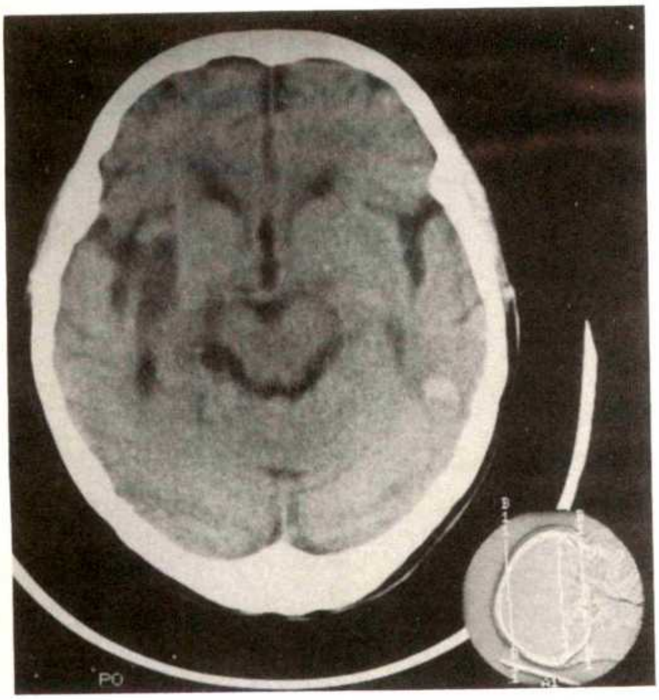


Figure 6 *Repeat computed tomogram after contrast agent injection at 30 days in patient shown in* Figure 5 *showing resolution of right temporoparietal haemorrhage; a further small haemorrhagic lesion is shown in the opposite (left) parietal area*

rt-PA over IA Sk therapy with regard to radiological lysis, subsequent risk of amputation and increase in ABPI. There were also significantly fewer haemorrhagic complications with IA rt-PA than with IA Sk, which is analogous to that seen when IV rt-PA is compared with IV Sk for coronary thrombolysis[21,29]. A further advantage of rt-PA is its non-antigenicity; repeated doses are feasible without increased risk of haemorrhage or allergic complication or, indeed, of the unpredictability which surrounds a second administration of Sk, due to a potentially profound antibody response. After over 700 patients have been treated with rt-PA worldwide, antibodies to rt-PA have been detected by radioimmunoprecipitation assay in only three samples. None had neutralizing antibodies, and in each case subsequent samples evaluated between 3 weeks and 10 months after treatment proved negative[30].

Concurrent low-dose heparin was given as part of both IA thrombolytic regimens to allow direct comparison of all laboratory and clinical parameters. However, we have subsequently shown that such addition is probably unnecessary and therefore we no longer recommend it[31].

The results of systemic administration of rt-PA were disappointing. Poor lysis was attended by a high incidence of haemorrhagic complications including one cerebrovascular accident. The relative 'fibrin-specificity' of rt-PA was compromised by systemic administration and by the higher doses administered, with a resultant intermediate effect on systemic activation. Accordingly, the haemorrhagic complications were significantly more than with low-dose IA rt-PA. This was probably due to a combination of increased lysis of the 'sealing' thrombus at venepuncture sites and to the increased systemic lytic state. Although the maximum allowable dose was the same for all subgroups in the IV rt-PA group, the rates of infusion varied from 1 mg to 10 mg/h. The likelihood of thrombolytic success, and that of a haemorrhagic complication, was evenly distributed throughout the subgroups.

In summary, this study suggests that IA rt-PA produces a more consistent, complete thrombolysis than conventional treatment with Sk. Although not totally 'fibrin-specific', it nevertheless offers a significantly lower systemic effect than Sk which is reflected in a lower incidence of haemorrhagic complications. The potential use of rt-PA as a systemic agent for peripheral arterial thrombolysis seems disappointing. Poor overall lysis rate combined with a high incidence of haemorrhagic complications show it to be unacceptable for routine use in this condition. Local IA low-dose thrombolysis remains the method of choice for peripheral arterial thrombolysis despite the availability of rt-PA, a new and relatively 'fibrin-specific' thrombolytic agent. This study also suggests that rt-PA may be a superior agent to Sk in this context.

Acknowledgements

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Infra-inguinal aneurysms: outcome for patient and limb

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The outcome of conservative treatment of infra-inguinal (femoral and popliteal) aneurysms was compared with that following vascular reconstruction. Over a 12-year period up to December 1988, 43 femoral aneurysms and 35 popliteal aneurysms presented to the Oxford Regional Vascular Service; 88 per cent of the femoral and 60 per cent of the popliteal aneurysms were treated by vascular reconstruction. The outcome was assessed in terms of limb symptoms or preservation and patient survival at the most recent point of follow-up (median 4·5 years). At least 12 of the 13 initially asymptomatic femoral and popliteal aneurysms which were untreated remained asymptomatic. In contrast, six of the 26 limbs with asymptomatic femoral aneurysms and three of the 11 limbs with asymptomatic popliteal aneurysms developed significant distal ischaemia after vascular reconstruction; four limbs came to amputation after intervention. Aggressive surgical management of all asymptomatic infra-inguinal aneurysms is unjustified and dangerous.

Aneurysms of the femoral and popliteal arteries are much less common than abdominal aortic aneurysms. They may threaten function or viability of the limb if they rupture, thrombose or shed distal emboli, but seldom pose a threat to life. Therefore, both elective and emergency surgery are usually limb-saving rather than life-saving. The primary objective in management of the patient with an infra-inguinal artery aneurysm is to conserve a fully functional limb until death. The aim of this study was to compare the outcome in patients treated by arterial reconstruction with that for those managed conservatively.

Patients and methods

Patients presenting to the Oxford Regional Vascular Service between 1 January 1977 and 31 December 1988 with a diagnosis of femoral or popliteal aneurysm were followed up until death The few too unfit to attend as outpatients were sent a questionnaire at the time of this study

The initial mode of presentation and treatment were noted. The subsequent outcome for the limb at the maximal follow-up time was classified as follows group A, asymptomatic – an intact limb with no symptoms of rest pain or claudication; group B, claudication; group C, rest pain; group D, amputation

Results

There were 52 patients with femoral and/or popliteal aneurysms; 43 femoral aneurysms occurred in 38 patients and 35 popliteal aneurysms in 26 patients. The median ages at presentation were similar, 64 years (range 20–92) and 65 years (range 27–92) respectively, as were the proportions of women, 10 and 8 per cent respectively. Thirteen (30 per cent) of the femoral aneurysms and eight (23 per cent) of the popliteal aneurysms occurred in patients who also had an abdominal aortic aneurysm.

The aetiology of the aneurysms is shown in *Table 1*. The false femoral aneurysms all followed local procedures in the groin as shown in *Table 2*. All but two of the 13 associated aortic aneurysms were found in patients with 'atheromatous' femoral aneurysms.

Presentation

Many aneurysms were noted incidentally The majority of symptomatic aneurysms produced only local discomfort and a few thrombosed, ruptured or caused distal embolization (*Table 3*). The category of 'distal ischaemia' in *Table 3* refers to those patients whose distal ischaemia was not obviously related to thrombosis of, or embolization from, the proximal aneurysm. Although the false femoral aneurysms in general followed surgery for stenotic disease, the majority of cases of distal ischaemia occurred in patients with true femoral aneurysms ($n=6$) rather than those with false aneurysms ($n=1$). The severity of ischaemic symptoms associated with the aneurysms is also shown in *Table 3*. Significantly more patients with popliteal aneurysms presented with rest pain than did those with femoral aneurysms ($P<0{\cdot}05$, $\chi^2=6{\cdot}08$). Five of the patients with rest pain associated with popliteal aneurysms had a thrombosed aneurysm.

Table 1 *Aetiology of aneurysms*

	'Atheromatous'	False	Mycotic
Femoral aneurysms	25	15	3
Popliteal aneurysms	34	0	1

Table 2 *Causes of false femoral aneurysms*

Cardiac catheterization	4
Femoral artery endarterectomy	3
Aortofemoral or iliofemoral graft	4
Femoropopliteal graft	3
Axillofemoral graft	1
Total	15

Table 3 *Symptoms at presentation*

	Femoral aneurysms	Popliteal aneurysms
Asymptomatic	16	12
Local discomfort	15	7
Rupture	3	1
Embolism	2	7
Thrombosis	0	6
Distal ischaemia	7	2
Claudication	6	2
Rest pain	1	8

Note: not all patients with distal embolization had claudication or rest pain

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Table 4 *Outcome for femoral aneurysms according to presentation and treatment*

	Group A ($n=5$)	Group B ($n=26$)	Group C ($n=0$)	Group D ($n=12$)
Asymptomatic	5	15	–	7
Claudication	–	1	–	3
Rest pain	–	2	–	–
Amputation	–	3	–	1
Unknown	–	5	–	1
Dead	1	11	–	5
Median age in years (range)	60 (63–74)	62 (20–92)	–	66 (53–77)
Median follow-up time in years (range)	2 (1/12–8)	4 (1–13)	–	4 (5/12–13)

Group A, asymptomatic/local discomfort, no surgery; group B, asymptomatic/local discomfort, with surgery; group C, symptomatic, no surgery; group D, symptomatic, with surgery

Table 5 *Outcome for popliteal aneurysms according to presentation and treatment*

	Group A ($n=8$)	Group B ($n=11$)	Group C ($n=6$)	Group D ($n=10$)
Asymptomatic	7	8	3	6
Claudication	–	2	–	3
Amputation	–	1	3	1
Unknown	1	–	–	–
Dead	7	1	5	5
Median age in years (range)	67 (55–92)	61 (27–73)	81 (58–84)	68 (55–81)
Median follow-up time in years (range)	6 (4–8)	3·5 (1–10)	3 (1/52–8)	4·5 (0·5–11)

Group A, asymptomatic/local discomfort, no surgery, group B, asymptomatic/local discomfort, with surgery; group C, symptomatic, no surgery; group D, symptomatic, with surgery

Treatment

No treatment was given for five (12 per cent) of the femoral aneurysms, all asymptomatic and all except one atheromatous. In eight of the false femoral aneurysms the defect was repaired by resuture. Eight femoral aneurysms were treated by aortobifemoral bypass and 22 with a local graft.

Fourteen (40 per cent) of the popliteal aneurysms were not treated by arterial surgery but three of these, all thrombosed, required immediate amputation for irreversible ischaemia. The remainder had bypass grafts to exclude the aneurysm, 15 of which were local grafts and six femoropopliteal bypass grafts

Outcome

Data were available on the outcome for all except six femoral and one popliteal aneurysms. Outcome was analysed according to presentation and intervention. Group A were asymptomatic or had only local discomfort at presentation and had no arterial surgery. Group B had a similar presentation but had arterial surgery. Group C comprised those patients with distal symptoms who did not have arterial surgery and group D were those with a ruptured aneurysm or distal symptoms who had arterial surgery. The results are shown in *Tables 4* and *5*. Although the median ages and follow-up times varied as shown, they did not differ significantly beween the groups. Significantly more of the asymptomatic patients with popliteal aneurysms who avoided intervention died during the follow-up period than did those asymptomatic patients who had reconstruction ($P<0{\cdot}01$, $\chi^2=8{\cdot}69$).

The outcome for limbs with femoral aneurysms could also be assessed according to the aetiology of the aneurysm. The three mycotic aneurysms and the four false aneurysms associated with cardiac catherization all did well; none had symptoms over follow-up of 2–8 years This is in marked contrast to the overall outcome for limbs with false aneurysms which fared relatively badly in general; only seven out of 15 were asymptomatic during follow-up whereas 17 out of 25 limbs with 'atheromatous' aneurysms were asymptomatic. Significantly more of the limbs with false aneurysms came to amputation (four out of 15) compared with those with 'atheromatous' aneurysm (none out of 25) ($P<0{\cdot}05$, $\chi^2=4{\cdot}74$).

It was not possible to assess the outcome for popliteal aneurysms on the basis of aetiology because all except one were 'atheromatous'. Six patients developed a clinically obvious deep venous thrombosis after bypass grafting for popliteal aneurysm.

Discussion

The majority of infra-inguinal aneurysms are asymptomatic or associated with only local discomfort at presentation. Popliteal aneurysms are more often associated with impaired limb viability than are femoral aneurysms, mainly because of aneurysm thrombosis. Many studies strongly advocate surgery in asymptomatic popliteal aneurysms to prevent future disasters[1–3]. However, those popliteal aneurysms in the present study which were asymptomatic at presentation remained so over several years and asymptomatic aneurysms treated surgically fared worse than those which were untreated.

This study suffers the same drawback as other retrospective reports in that the asymptomatic unoperated patients were a selected group. In earlier studies[1–3] the aneurysms tended to be large and the indication for non-intervention was generally the poor state of health of the patient. Nearly 30 per cent of their asymptomatic non-operated patients developed aneurysm-associated complications over the next 4–5 years. In the study by Whitehouse *et al.*[4] small aneurysm size in addition to poor general condition was an indication for non-intervention in the asymptomatic aneurysm. Fewer than 18 per cent of this group developed significant distal ischaemia. A more recent study[5] reported an 8 per cent complication rate over 3 years in patients selected for non-operation mainly on the basis of small aneurysm size. In the present study, size was not recorded in all cases but the asymptomatic popliteal aneurysms were selected for non-intervention mainly on the basis of small size. It is questionable, however, whether aneurysm size is an important determinant in predicting complications, since several authors have found that the incidence of aneurysm thrombosis, at least, is unrelated to aneurysm size[6,7] and may even be higher in small aneurysms[8]. A better guide to future problems may be the presence of thrombus within the aneurysm, detectable by ultrasound or computerized tomography scanning[9,10].

The median age of our patients with popliteal aneurysm was 65 years and the mortality rate was high as with all patients with vascular disease; 51 per cent died over a median period of 4·5 years. A high mortality rate during follow-up has been reported by others[3]. If time is an important factor in producing symptomatic limb ischaemia with these aneurysms, then many will die before they become symptomatic.

As with asymptomatic popliteal aneurysm, patients with asymptomatic femoral aneurysm did no better, and possibly worse, with surgical intervention than without surgery. In the present study the asymptomatic unoperated aneurysms were almost all atheromatous. Other studies support a non-intervention policy in these aneurysms, particularly if they are small[11,12]; a similar approach has also been advocated for asymptomatic false aneurysms[13]. Once they become symptomatic, however, patients with femoral aneurysms do badly whether or not they are operated on, and particularly if they have false aneurysms secondary to previous surgery for stenotic disease.

A policy of operating on all asymptomatic infra-inguinal aneurysms is unjustified and potentially dangerous; many which are asymptomatic remain so over several years and the expected lifespan of these patients is often short. Selective surgical treatment, based on symptoms, the amount of mural thrombus, the diameter of the aneurysm and the life expectancy of the patient, is likely to produce better results. This is reinforced by the improved outcome which can now be obtained[14] with modern thrombolytic therapy in aneurysms which do eventually thrombose.

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Observed incidence of paraplegia after infrarenal aortic aneurysm repair

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The incidence of paraplegia or paraparesis after repair of aortic aneurysm depends primarily on the anatomical location. For types I and II thoracoabdominal aneurysm the incidence is 34 per cent; for types III and IV it is 5·2 per cent[1]. Paraplegia is much less common after repair of infrarenal aortic aneurysm; indeed up to 1956 no case had been described[2]. Two recent cases in Oxford prompted a questionnaire to eight other centres in the UK to assess the overall incidence of this distressing complication of infrarenal aortic surgery.

Case reports

Case 1

A 76-year-old man was admitted for elective repair of a 7·2 cm asymptomatic abdominal aortic aneurysm He was a diet-controlled diabetic, hypertensive and had not smoked for 40 years He had ischaemic heart disease and mild bilateral claudication. There were no neurological symptoms.

In a routine uneventful operation an aortobiliac graft was anastomosed end-to-end to the infrarenal aorta and end-to-side to the external iliac arteries. The patient required no blood transfusion and his blood pressure remained stable throughout the operative and postoperative period. The following day he had a flaccid total paralysis of both legs, absent leg reflexes and a sensory deficit up to the level of T12. There was no subsequent neurological improvement.

Case 2

A 67-year-old man underwent surgery for an asymptomatic 6 2 cm abdominal aortic aneurysm associated with atheromatous occlusion of the right iliac system A bifurcated graft was anastomosed end-to-end to the infrarenal aorta, the left common iliac artery and the right profunda femoris artery. The operation took 4 h because of technical difficulties at the right groin but inflow to the left common iliac system down the graft was established after 30–40 min of clamp time The patient was transfused with 2 litres of blood but had no hypotensive episode during the operation.

He was extubated the following day and a lumbar epidural catheter was placed for postoperative analgesia. Later the same day he became hypotensive and over the next 12 h required intravenous infusion of a substantial volume of fluid to maintain central venous pressure. An exploratory laparotomy revealed no cause for the hypotension which was eventually attributed to septicaemia Subsequently he developed acute tubular necrosis, required mechanical ventilation for 5 days and labetalol to control his blood pressure. As he was weaned off the ventilator it was noticed for the first time that there was a flaccid paralysis of the right leg and paresis of the left leg Sensation was impaired below the T12 level A myelogram showed no evidence of spinal cord compression. In the 6 weeks after surgery he recovered renal function, developed a hypotonic bladder and recovered some power in both legs

Questionnaire

Questionnaires were sent to eight other vascular units in the UK requesting their incidence of paraplegia following infrarenal aortic surgery and details of the nature and circumstances of the surgery. The pooled information from these centres revealed eight cases of paraplegia; four occurred after emergency repair of an aortic aneurysm, two after elective repair of an aortic aneurysm and two after aortobifemoral or aortobiprofunda bypass for occlusive disease. The total figures for infrarenal aortic grafts in the time the cases occurred was 7156, an incidence of 0·11 per cent. A suprarenal clamp was in place for 20 min during one emergency repair of a ruptured aneurysm but there were no features of the other cases which distinguished them from the majority of uncomplicated operations.

In Oxford during the past 5 years, 244 patients have undergone elective infrarenal aortic surgery with two cases of paraplegia, an incidence of 0·8 per cent. In the same time there has been no case of paraplegia in any of the 90 patients who survived surgery for ruptured abdominal aortic aneurysm. The overall observed incidence of paraplegia after infrarenal aortic surgery has therefore been 0·6 per cent.

Discussion

Paraplegia following infrarenal aortic aneurysm repair has been the subject of scattered case reports in the literature[3–8] The largest numbers reported from single institutions are eight by Szilagyi *et al.*[9] in 1978 and seven by Picone *et al.*[10] in 1986 These figures yielded incidences of 0·25 per cent and 0·9 per cent respectively. Collected reviews[11,12] suggest that about 50 per cent occur after repair of a ruptured aneurysm and a third after elective aneurysm repair; relatively few occur after grafts for aortic occlusive disease[8]

The cause of paraplegia after aortic surgery will, in the great majority of cases, be spinal cord ischaemia, but the possibility of spinal cord compression should not be overlooked Spinal cord compression can be excluded with confidence only by computed tomography, magnetic resonance imaging or myelography, and a strong case can be made for performing one or other of these investigations in all affected patients. The justification for such an approach is that spinal cord compression is a treatable and potentially curable cause of paraplegia while spinal cord ischaemia is not.

Paralysis from spinal cord ischaemia usually derives from T12–L2 level, but is occasionally higher. There are several possible reasons for spinal cord ischaemia The cord is supplied predominantly by the anterior spinal artery. Although there are two posterior spinal arteries, their combined territory is small and is less often affected in cases of paraplegia. The anterior spinal artery is supplied by the vertebral arteries, supplemented along its length by generous contributions from six to eight segmental arteries arising from intercostal or lumbar arteries The lowest of these is the artery of Adamkewicz, which arises from the lower thoracic or upper lumbar aorta and usually makes an important contribution to lower cord blood supply. Estimates of the frequency with which it arises from the infrarenal aorta vary from 50 per cent[13] to less than 25 per cent[14]. In addition, the iliolumbar and lateral and median sacral arteries contribute to cord blood supply.

Much importance has been ascribed to the artery of Adamkewicz with regard to the development of paraplegia in lower aortic surgery[3–7,9] If it lies below the renal arteries, or if a suprarenal clamp is applied for a substantial time above it, it is likely to occlude Obviously other factors are also important, otherwise the incidence of spinal cord damage would be higher. The degree of reliance on the artery of Adamkewicz, the amount of collateral vessel development, and the quality of perfusion in these vessels are all important There is often atheromatous narrowing of the origins of the lumbar vessels and this may promote collateral development. The lower incidence of paraplegia after bypass for stenotic aortic disease

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is probably related to the greater degree of collateral development. Paraplegia may follow a period of hypotension, either before operation, e.g. in ruptured aortic aneurysm, or later, suggesting thrombosis of the collateral circulation.

The spinal cord is not the only tissue at risk. The inferior mesenteric artery is often ligated during surgery and an ischaemic left colon has often been reported in association with paraplegia[5,6,9–11]. This may reflect the generalized impairment of the collateral circulation but a more direct link may be the reliance of both areas on the internal iliac arteries for blood supply. Picone *et al.*[10] found that five of their seven cases occurred when internal iliac artery perfusion was reduced or completely absent. They stress the importance of the internal iliac artery supply to the spinal cord via the iliolumbar and lateral sacral vessels.

The onset of paraplegia is usually immediate but diagnosis may be delayed when pharmacological paralysis and mechanical ventilation are required after operation. There are a few well-documented cases[10,15] in which the onset was genuinely delayed for up to 48 h. In a few cases, a period of hypotension may precede the onset of paraplegia[15]. Autopsy in some cases of delayed onset[15] has revealed an aortic dissection, extending proximally from the upper anastomosis and occluding proximal lumbar vessels, or thrombus lining the graft and extending proximally in the aorta, again occluding proximal branches.

Approximately 50 per cent of patients make no neurological recovery. The remainder make a full or partial recovery, sensation often returning before motor function[12].

Manoeuvres to avoid spinal cord ischaemia are common in thoracic aortic surgery. Measures such as the administration of opiate antagonists and steroids together with cerebrospinal fluid drainage and re-implanting of large lumbar arteries may be helpful[16]. In infrarenal aortic surgery it is wise to preserve internal iliac artery perfusion if possible, as the incidence of this relatively rare but devastating complication appears to be more common when internal iliac inflow is sacrificed[9].

The relatively low apparent incidence of this complication when calculations are based on hearsay evidence amassed from several centres is in contrast to the incidence calculated from audited records of a single institution which range from 0·25 per cent[9] to 0·9 per cent[10], and our own figure of 0·6 per cent. Despite these doubts it can confidently be concluded that the risk of paraplegia after aortic surgery confined to the infrarenal segment is less than 1 per cent; it is therefore reasonable not to warn the patient of this complication specifically when informed consent to operation is being sought.

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Comparison of iliofemoral and femorofemoral crossover bypass in the treatment of unilateral iliac arterial occlusive disease

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Between 1981 and 1988, 74 synthetic crossover bypass grafts were inserted for unilateral iliac arterial occlusive disease. In 32 patients the bypass procedure was iliofemoral and in 42 femorofemoral. The cumulative patency rate at a mean of 2·7 years was 79 per cent in both groups. There was no significant difference in either postoperative mortality rate or duration of hospital stay. Iliofemoral bypass may offer significant advantages over the femorofemoral approach. In particular it avoids a groin incision in the donor limb, leaving the common femoral artery intact for subsequent angioplasty or reconstruction should proximal stenotic disease develop in the donor iliac vessel.

Because of its simplicity and reported durability, femorofemoral crossover bypass is a reasonable alternative to aortofemoral reconstruction for unilateral iliac arterial occlusive disease[1]. The indications for this approach have widened[2] from high-risk patients to all patients with unilateral iliac arterial disease[3,4]. An alternative approach has been advocated using the external iliac artery as the donor vessel, rather than the common femoral, thereby avoiding a groin incision on the donor side[3,5]. This report is an analysis of crossover bypass procedures performed in this unit between 1981 and 1988.

Patients and methods

A total of 74 patients with unilateral iliac arterial occlusive disease were treated between March 1981 and December 1988. The patients were randomly allocated to either an iliofemoral crossover or a femorofemoral crossover bypass procedure, 42 having a femorofemoral bypass and 32 an iliofemoral bypass. There were 53 men (mean age 61 years, range 38–78 years) and 21 women (mean age 67 years, range 38–83 years) Synthetic grafts were used in all cases.

The indications for surgery were disabling claudication ($n = 39$) and rest pain ($n = 35$). Of the latter, three had pregangrene, three ischaemic ulcers and two established gangrene of one or more toes Eighteen grafts were inserted as a secondary procedure to unilateral iliac limb thrombosis after previous aortoiliac reconstruction These included aortobifemoral bypass (12 procedures), aortoiliac endarterectomy (three procedures), ipsilateral iliofemoral bypass (one procedure) and aortic aneurysm reconstruction (two procedures)

Eighteen patients (24 per cent) had a previous history of myocardial infarction or angina, two (3 per cent) had had previous cerebrovascular accidents. There were ten diabetics (14 per cent), and 44 patients (59 per cent) had no significant relevant previous history. There was no significant difference in the incidence of these previous events between the groups

To be selected for crossover bypass, the patient was required to have a strong common femoral pulse in the asymptomatic leg, an absent or grossly reduced pulse in the symptomatic leg, and angiographic confirmation of severe unilateral occlusive iliac disease not amenable to angioplasty or a failed attempted previous iliac angioplasty

A combination of preoperative angioplasty followed by a crossover bypass was performed if there was a significant pressure drop across a stenosis in the donor iliac vessel (18 patients) Preoperative arteriography was performed for 68 patients In previous studies[6,7] up to 30 per cent of patients did not undergo preoperative arteriography. However, we believe that arteriography is to be recommended to detect this significant group of patients (24 per cent) who could benefit from donor limb angioplasty either before operation or at the time of operation.

A conventional exposure of the common femoral vessel and its branches was performed. In the iliofemoral group, a small muscle-splitting incision on the side of the donor iliac artery was placed parallel to and above the inguinal ligament and the external iliac artery was approached extraperitoneally. Heparin 5000 units was given intravenously and arterial control was established An 8 mm synthetic graft (either Meadox Verisoft® Dacron (Meadox, Dunstable, UK) or Gore-Tex® (externally supported polytetrafluoroethylene, W L Gore and Associates Incorporated, Woking, UK)) was tunnelled extraperitoneally (in both groups) or subcutaneously (in the femorofemoral bypass group) when the patient was obese The anastomoses were performed using continuous 4/0 Ticron® (Davis and Geck, Effen Leur, The Netherlands). Before completing the anastomoses, an embolectomy catheter was passed into the superficial femoral (if patent) and profunda vessels on both sides If the profunda femoris was stenosed, a profundoplasty using the graft anastomosis or a separate profundoplasty was performed.

After operation, patients were routinely prescribed aspirin 150 mg/day and dipyridamole 100 mg three times a day. Patients were reviewed after 6 weeks and then at intervals of 6 months Graft patency was determined by the presence of a palpable groin pulse in the previously symptomatic leg. Doppler studies (ankle artery pressure) were routinely performed and compared with preoperative findings When graft patency was in doubt, arteriography was performed.

Results

Of the 74 patients who entered the study, five died A further two patients were lost to follow-up after discharge The remaining 67 patients were followed for a mean of 32 5 months In the immediate postoperative period 46 patients had no complications. Ten patients developed chest infection, ten had superficial wound infection and two (femorofemoral group) developed false aneurysms at 8 months and 2 years after operation. Both of these were successfully repaired. There was no graft infection Mean hospital stay after operation was 7·4 days (range 5–11 days)

Iliofemoral crossover bypass group (32 patients)

Three patients died: one from myocardial infarction on the third day after operation, one from a massive bleed from a duodenal ulcer 1 month after surgery, and one from carcinomatosis 3 months after bypass. One patient was lost to follow-up A further patient underwent successful aortobifemoral bypass after the original crossover graft failed. Five patients came to amputation, two within 30 days of reconstruction and three within a year. At the end of the follow-up period (mean 2 7 years) 22 grafts were patent with a mean cumulative patency rate of 79 per cent

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Femorofemoral crossover bypass group (42 patients)

Two patients died, one from myocardial infarction on the second day after operation and one suddenly while on holiday abroad. One patient was lost to follow-up. One femorofemoral graft occluded, but both limbs remained viable. Eight patients came to amputation, two within 30 days of bypass, two after 2 months, and four within a year. At the end of the follow-up period (mean 2·7 years), 30 grafts remained patent with a mean cumulative patency rate of 79 per cent.

Discussion

Crossover bypass is a safe procedure which can be performed expeditiously (in less than 1 h) and, if necessary, under regional anaesthesia[8]. The mortality rate for a crossover bypass ranges from 0 to 15 per cent[7]. In this study there were five perioperative deaths (7 per cent). There was no significant difference in postoperative mortality rate, duration of hospital stay or cumulative patency rate between the two types of crossover procedure.

The choice of graft material is probably not important[9]. Initially, a knitted Dacron graft was used, but later in the study an externally supported polytetrafluoroethylene graft was employed. Although others[10,11] have noted a predominance of left-sided iliac arterial stenotic disease, we have found almost equal involvement of the right (36 patients) and left sides (38 patients)[6].

Although iliofemoral crossover and femorofemoral crossover bypass procedures serve the same purpose, by using the iliac artery as the donor conduit for the bypass the graft anastomosis is placed outside the groin and therefore does not damage groin lymphatics. There is a lower risk of contamination and the inguinal incision generally permits uncomplicated healing. The iliac anastomosis may also protect the graft from traction on the anastomosis, which may be responsible for anastomotic aneurysm formation[5]. A further bonus of the iliac procedure is that the donor limb common femoral artery remains virginal for subsequent arteriography, angioplasty or further reconstruction if progressive disease develops in the donor iliac system[3,12,13]. For these reasons, we conclude that the iliofemoral crossover procedure is the operation of choice

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Value of duplex scanning compared with angiography and pressure measurement in the assessment of aortoiliac arterial lesions

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To detect haemodynamically significant lesions in the aortoiliac arteries, invasive tests such as angiography and intra-arterial pressure measurement (IAPM) are considered valuable diagnostic tools. The value of duplex scanning as a direct non-invasive examination technique was prospectively compared with intra-arterial digital subtraction angiography (IADSA) and IAPM at rest, and after the administration of papaverine in 60 patients. Excellent agreement, as assessed by the κ statistic, was shown between duplex scanning and IADSA ($\kappa = 0{\cdot}81$). A fair agreement was shown between duplex scanning and IAPM ($\kappa = 0{\cdot}63$), and between IADSA and IAPM ($\kappa = 0{\cdot}63$). Duplex scanning and IADSA both missed some less haemodynamically critical lesions if IAPM was considered the 'gold standard'. It is concluded that duplex scanning detects haemodynamically significant lesions as effectively as angiography and so may be considered a new and valuable diagnostic tool. IAPM remains necessary to detect some lesions of borderline haemodynamic significance. However, with future developments, duplex scanning has the potential to replace the need even for IAPM.

To assess the severity of atherosclerotic lesions in the aortoiliac arteries, angiography and intra-arterial pressure measurement (IAPM) are still considered the most accurate diagnostic tools. However, angiography provides only morphological data, whereas IAPM provides functional information about the severity of lesions, and therefore the latter may be considered the 'gold standard'[1]. This is particularly evident in patients with less critical aortoiliac stenoses in whom postoperative improvement is considered the best standard to which the preoperative diagnostic tests may be compared[2,3]. However, IAPM is not always considered necessary in clinical decision-making with regard to therapeutic intervention. This is mainly because the angiographic findings can be easily correlated with the clinical symptoms of the patient.

There is increasing interest in duplex scanning as a powerful non-invasive examination technique for the detection of intravascular lesions. This technique is already extensively used in the evaluation of carotid artery disease, in which it has equalled or outrun the imaging standard of angiography[4]. Few studies have examined the value of duplex scanning in the assessment of atherosclerotic lesions in the aortoiliac arteries[5–11]. Although the use of this diagnostic technique in this part of the arterial tree is still evolving, some of these studies suggest that duplex scanning might be as precise as angiography and have the potential to replace angiography.

To compare the value of duplex scanning with angiography and IAPM in the detection of haemodynamically significant lesions in the aortoiliac arteries, we prospectively studied 60 patients using duplex scanning, triplane intra-arterial digital subtraction angiography (IADSA) and IAPM.

Patients and methods

Duplex scanning of the infrarenal aorta and iliac arteries was performed in 60 patients with claudication, rest pain or arterial ulcer disease. This was followed within 1 day, in all but one patient, by IADSA and IAPM before and after the administration of papaverine.

Duplex examinations were performed by one of two vascular technologists at the beginning of the series with an ATL Mark V® and later on with an ATL Ultramark IV duplex scanner® (Advanced Technology Laboratories, Washington, USA). Patients fasted for at least 6 h before examination to minimize problems related to excessive bowel movement and gas. Examination was performed with the patient supine. The probes used were 3 or 5 MHz imaging probes and 3 or 5 MHz single-gate pulsed Doppler probes, as appropriate. The use of 3 MHz imaging and Doppler probes is essential if deep duplex scanning is needed, e.g. in an obese or gaseous abdomen. In suitable patients, examination can also be performed with 5 MHz probes, which increases image quality.

The detection by duplex scanning of a stenosis of less than or more than 50 per cent diameter reduction was based on the relative change in peak systolic velocity (PSV) at the site of a lesion compared with the pre-stenotic and post-stenotic PSV in the same arterial segment[10]. The change in PSV at the site of a stenosis is directly related to the reduction in cross-sectional area of the blood vessel and can be expressed as a ratio:

$$\text{PSV ratio} = \frac{\text{PSV in stenosis}}{\text{Pre-stenotic or post-stenotic PSV}}$$

The lowest PSV value, pre-stenotic or post-stenotic, was used as the denominator for definitive analysis. If a lesion was localized at the origin of an arterial segment, the post-stenotic PSV was always taken as the denominator.

To differentiate between less than or more than 50 per cent diameter reduction, duplex criteria were defined as follows: a PSV ratio of less than 2·5 correlated to a diameter reduction of less than 50 per cent, a PSV ratio of greater than or equal to 2·5 indicated a 50–99 per cent diameter reduction. Absence of any Doppler signal indicated occlusion. A lesion was considered to be of possible haemodynamic significance if the PSV ratio was greater than or equal to 2·5 or the Doppler signal was absent.

IADSA was performed by the Seldinger technique. A transiliac catheter with an external diameter of 5 Fr was inserted via an introduction sheath with an internal diameter of 7 Fr placed in the common femoral artery up into the aorta. Angiographic recordings were made in the anteroposterior and left and right oblique views. Lesions were considered to be of possible haemodynamic significance if the diameter reduction of the artery on the angiogram was greater than or equal to 50 per cent in at least one of the three views

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Intra-arterial pressures were measured at the end of the angiographic procedure at rest and after the intra-arterial administration of 50 mg papaverine via the common femoral artery. Pressures in the aorta and in the common femoral artery were simultaneously recorded by coaxial pressure measurement via the introduction sheath and intra-aortic catheter. The contralateral common femoral artery was cannulated separately. Pressure measurements were graphically and digitally displayed. An absolute peak systolic aortofemoral pressure gradient greater than 20 mmHg at rest or a decrease in femoral·aortic pressure index of greater than or equal to 15 per cent after the administration of papaverine was considered haemodynamically significant.

All but two angiograms and IAPMs were performed and read by the same radiologist. The radiologist and vascular technologist were unaware of the outcome of the other's tests. The existence of one or more possibly haemodynamically significant lesions was considered a positive test result for that specific test. Results for the different tests were evaluated in two-way contingency tables. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy were calculated. For each table, the κ statistic was estimated to correct for agreement beyond chance. Values below κ = 0·40 represent poor agreement, between 0·40 and 0·75 represent fair to good agreement, and greater than 0·75 excellent agreement[12].

Another part of the study attempted to analyse whether further separation of lesions by duplex scanning in the clinically important range of greater than or equal to 50 per cent diameter reduction, as determined by angiography, would be possible. Therefore, angiographic lesions were further divided into those producing 50–74 per cent, 75–99 per cent and 100 per cent diameter reduction, and were compared to the results of two spectral analysis criteria measured by duplex scanning. The first criterion for comparison was the PSV ratio, which was expected to increase as the lesion became more severe. The second criterion was the end diastolic velocity (EDV), which was predicted to be of value in the detection of lesions of 75–99 per cent diameter reduction[7,10]. Receiver operating characteristic analysis was used to find the PSV ratio or EDV which would be most useful in differentiating between 50–74 per cent and 75–99 per cent diameter reduction. For the purpose of analysis, the aortoiliac tract was subdivided into the infrarenal aorta, common iliac and external iliac arterial segments.

Table 1 *Two-way contingency table*

	Pressure		
	–	+	Total
Angiography			
–	47	14	61
+	6	41	47
Total	53	55	108
Duplex			
–	47	14	61
+	6	41	47
Total	53	55	108

κ=0·63 (95 per cent confidence limits 0·49–0·78) for both angiography *versus* pressure and duplex *versus* pressure. –, No significant lesion, +, significant lesion

Table 2 *Two-way contingency table, results of duplex scanning* versus *angiography*

	Angiography		
Duplex	–	+	Total
–	56	5	61
+	5	42	47
Total	61	47	108

κ=0·81 (95 per cent confidence limits, 0·70–0·92). –, No significant lesion, +, significant lesion

Results

Of the 120 aortoiliac sides in 60 patients, 12 were excluded from final evaluation. Four patients had a haemodynamically significant aortic lesion; in these patients only one side was included for data analysis. In four tracts, duplex scanning was technically unsuccessful and it could not be judged whether a haemodynamically significant lesion existed or not. In three segments a meaningful PSV ratio could not be reached because a very high pre-stenotic and post-stenotic velocity was measured, most probably due to severe stenosis of the entire arterial segment. One of the two IAPMs was not technically possible in one patient.

The results of duplex scanning and angiography compared to pressure measurements are shown in *Table 1*. Coincidentally, values in both tables are the same. The relatively high number of false-negative angiographies and duplex scans, both 14, is striking if pressure is considered the gold standard. Twelve of these 14 were underestimated, both on duplex scanning and angiography. Of the six false-positives, three were false-positive on duplex scan as well as angiography.

The concordance between duplex scanning and angiography is shown in *Table 2*. False-positives and false-negatives are equally distributed. Interestingly, if angiography is considered the diagnostic standard to which duplex scanning is compared, three false-negative duplex scans also did not show a significantly increased pressure gradient. Of the five false-positive duplex scans, two also showed a significantly increased pressure gradient.

Sensitivity, specificity, PPV, NPV and accuracy with regard to several combinations of tests and diagnostic standards are shown in *Table 3*. The κ value of duplex scanning as compared to angiography is 0·81. Sensitivity, specificity, PPV, NPV and accuracy are all about 90 per cent. If duplex scanning and angiography are compared to pressure measurements, the κ value is 0·63 in both cases. If pressure measurement is considered the diagnostic standard and duplex scanning or angiography the test, sensitivity and NPV for both combinations are 75 per cent and 77 per cent, respectively. Specificity, PPV and accuracy are over 80 per cent.

For further comparison of duplex scanning with angiography, separation of the aortoiliac tract into the three different arterial segments yielded 270 segments for definitive analysis. Results for the different groups of diameter reductions are shown in *Table 4*. PSV ratios in the group with 75–99 per cent stenosis were markedly higher (median 5·0, 90 per cent range 2·7–15·0) compared with those in the group with 50–74 per cent stenosis (median 3·0, 90 per cent range 1·3–6·2). The median EDV for 75–99 per cent diameter reduction was 0·5 m/s (90 per cent

Table 3 *Results of several combinations of tests and diagnostic standards in the detection of a haemodynamic lesion*

Test	Diagnostic standard	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)	κ
IADSA	Pressure	75	89	87	77	81	0·63
Pressure	IADSA	87	77	75	87	81	0·63
Duplex	Pressure	75	89	87	77	81	0·63
Duplex	**IADSA**	**89**	**92**	**89**	**92**	**91**	**0·81**

IADSA, Intra-arterial digital subtraction angiography; PPV, positive predictive value; NPV, negative predictive value range 0·0–1·6 m/s) compared with a median of 0·0 m/s (90 per cent range 0·0–0·5 m/s) for lesions of 50–74 per cent diameter reduction. Receiver operating characteristic analysis showed that it was not possible to find a reliable cut-off level based on PSV ratios or EDV to discriminate between 50–74 per cent and 75–99 per cent stenosis for clinical decision-making. The use of a higher sensitivity was at the cost of too low a PPV (less than 80 per cent). Even the combination of these two spectral analysis criteria only slightly enhanced the sensitivity. Most useful values were obtained for a PSV ratio of greater than or equal to 5·5 and an EDV of greater than or equal to 0·6 m/s. Sensitivities, specificities, PPV, NPV and accuracies in the detection of lesions of greater than or equal to 75 per cent diameter reduction are shown in *Table 5*. Angiography showed an occlusion in seven arterial segments. These were all detected by duplex scanning. There were no false-negative or false-positive occlusions on the duplex scan.

Discussion

Several non-invasive tests are available to assess the severity of aortoiliac arterial lesions. So far, none has succeeded in replacing the need for angiography or IAPM for clinical decision-making with regard to therapeutic intervention. This is mainly because non-invasive tests are indirect and cannot accurately localize the site of a lesion. Furthermore, few of these tests are sufficiently accurate to differentiate between haemodynamically significant or insignificant aortoiliac arterial lesions. Duplex scanning is the first non-invasive diagnostic test which enables both accurate localization of a lesion and grading of stenoses (*Figures 1, 2* and *3*). In this study, duplex scanning was found to be highly accurate and comparable to angiography in determining the existence of aortoiliac lesions of more than 50 per cent diameter reduction. In our experience it was almost always possible to visualize the different segments of the aortoiliac arteries and to obtain adequate Doppler samples for analysis. Failure of adequate imaging was usually due to sonographic reflections from a severely calcified wall or to an obese or gaseous abdomen.

The existence of a lesion reducing the diameter by more than 50 per cent on the angiogram or duplex scan and its possible haemodynamic significance was chosen as a suitable criterion with which to compare these techniques because experimental work has shown that such lesions cause reductions in flow and distal pressure[13–16]. In this study it was shown that 75 per cent of lesions which were haemodynamically significant in terms of pressure measurement were indeed detected by angiography or duplex scanning. The agreement between duplex scanning and IAPM, however, was not as close as that between duplex scanning and angiography. This is indicated by the lower κ value of 0·63 compared with 0·81, lower sensitivity and NPV. A lower correlation was also found between angiography and pressure measurement, so that duplex scanning and angiography gave comparable results.

The marked agreement between duplex scanning and angiography with regard to the relatively high number of false-negative test results in the aortoiliac tract is probably a result of the failure of both tests to detect some less critical lesions. In six out of the 12 haemodynamically significant lesions which were missed using angiography and duplex scanning, a significant pressure gradient was found only after the administration of papaverine, and not in the resting state. This supports the idea that duplex scanning and angiography are highly comparable to each other.

Another conclusion from this study is that some borderline lesions will only be detected by pressure measurement after the administration of papaverine, and not by pressure measurement at rest, or by duplex scanning, or even triplane angiography. These findings are in accordance with theoretical considerations about these diagnostic procedures. Although duplex scanning measures PSV, which is a flow-dependent parameter, it should be realized that the information obtained by calculating a PSV ratio is directly related to the changes in diameter at the site of the lesion and is essentially flow-independent. In this way, duplex scanning as well as angiography provides only morphological data; it does not provide functional information about the haemodynamic significance of a stenosis. This is in contrast with measured pressure gradients which are directly related to flow and will thus increase if flow is enhanced by administration of papaverine. This is the reason that haemodynamically less critical lesions were only detected after the administration of papaverine and not by duplex scanning or angiography. Hence, the haemodynamic significance of an arterial stenosis in the aortoiliac segment detected by angiography or duplex scanning should be considered in relation to the proximal and distal arteriographic findings and clinical symptoms of the patient. If these considerations do not allow satisfactory conclusions, IAPM should be performed, and, if indicated, also after the administration of papaverine.

Although IAPM may be considered the 'gold standard', it should be realized that the magnitude of a pressure gradient depends on several factors, such as flow rate, upstream pressure and downstream resistance[16–18]. Some of these factors also

Table 4 *Two-way contingency table of duplex scanning based on PSV ratios, EDV and absence of Doppler signal* versus *angiography*

	Angiography diameter reduction				
PSV ratio	0–49%	50–74%	75–99%	100%	Total
Duplex					
<2·5	**209**	8	0	0	217
≥2·5 and <5·5	8	**15**	9	0	32
≥5·5 and/or EDV ≥0·6 m/s	0	2	**12**	0	14
No Doppler signal	0	0	0	**7**	7
Total	217	25	21	7	**270**

$\kappa = 0·70$ (95 per cent confidence limits 0·61–0·80). PSV, Peak systolic velocity; EDV, end diastolic velocity

Table 5 *Results of duplex scanning* versus *angiography in distinguishing between less or more than 75 per cent diameter reduction*

Spectral criteria ≥75 per cent	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)
PSV ≥5·5 or absence of Doppler signal	57	99	89	95	95
EDV ≥0·6 m/s or absence of Doppler signal	61	100	94	96	96
PSV ≥5·5 and/or EDV ≥0·6 m/s or absence of Doppler signal	68	99	90	96	96

There were 28 arterial segments with greater than or equal to 75 per cent reduction in diameter. Seven occlusions are included. PSV, Peak systolic velocity; EDV, end diastolic velocity; PPV, positive predictive value; NPV, negative predictive value

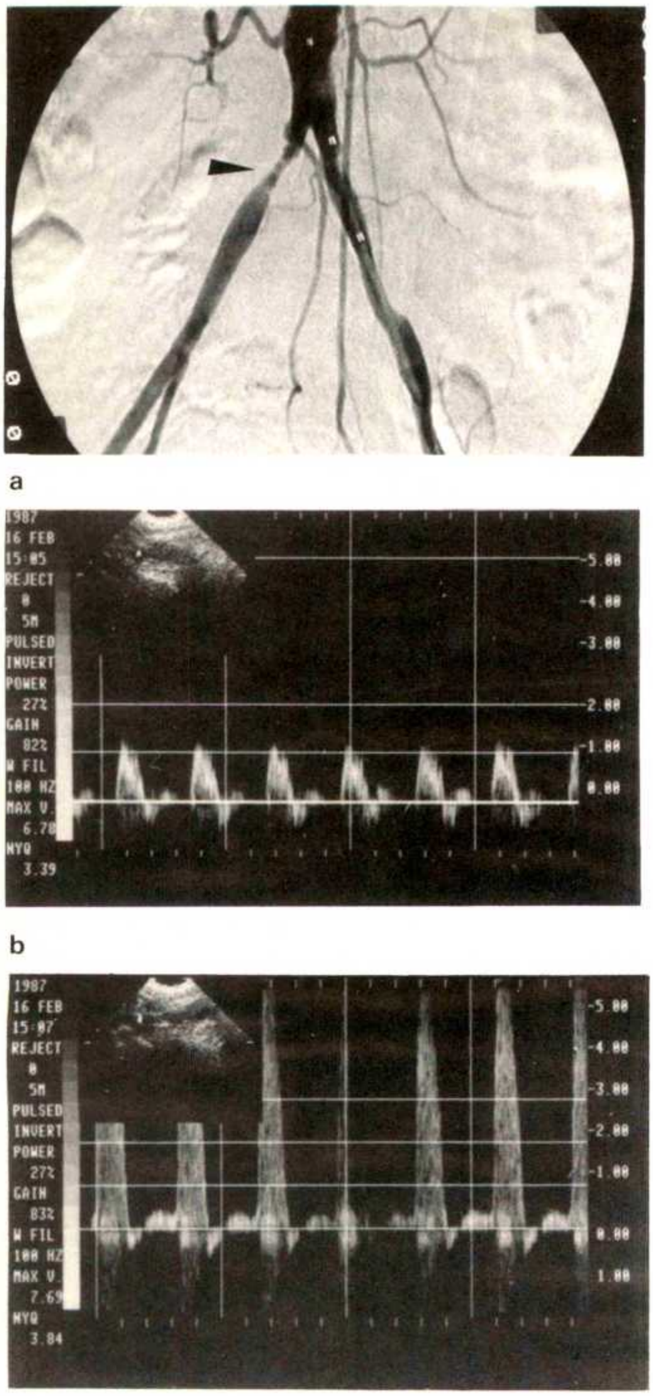

Figure 1 **a** *Angiogram showing greater than 50 per cent diameter reduction in right common iliac artery;* **b** *Doppler ultrasound component of duplex scan for prestenotic segment of right common iliac artery. Vertical axis represents velocity; horizontal axis represents time. Peak systolic velocity here is 1·1 m/s;* **c** *Doppler ultrasound component of duplex scan within the stenosis. Peak systolic velocity here is greater than 5·5 m/s. In conjunction with the value from (b) this gives a peak systolic velocity ratio of greater than 5·0*

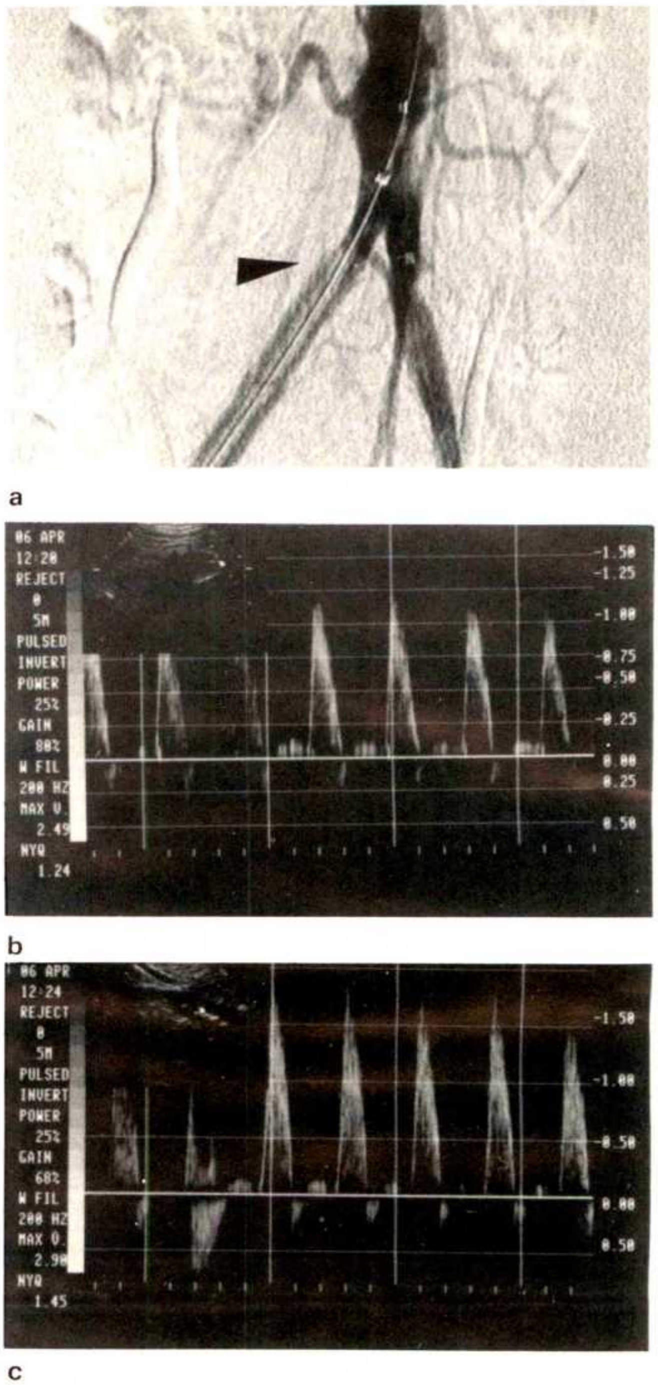

Figure 2 **a** *Same patient as in* Figure 1. *Angiogram showing right common iliac artery after percutaneous transluminal angioplasty;* **b** *Doppler ultrasound component of duplex scan for prestenotic segment of right common iliac artery* (Figure 1b). *Peak systolic velocity here is 1·2 m/s;* **c** *Doppler ultrasound component of duplex scan within the dilated area of artery. Peak systolic velocity is 1·8 m/s, giving a peak systolic velocity ratio of 1·5. This indicates a good result from angioplasty*

depend on the cardiovascular condition of the patient. That IAPM is not always the best diagnostic standard is illustrated by the lack of uniformity in the literature in defining the cut-off pressure gradient for haemodynamic significance, and also not if the postoperative result is considered the gold standard. In this study, the cut-off value of 20 mmHg at rest represents a mean between several recommended values in the literature[1]. A cut-off value after the administration of papaverine as recommended by Flanigan *et al.*[2] was used. Flanigan *et al.* prospectively compared IAPM with postoperative results. However, the technique was slightly different in that they used a non-invasively measured brachial peak systolic blood pressure instead of an invasively measured peak systolic aortic pressure; they used 30 mg papaverine instead of 50 mg. In the present study there were three cases in which both duplex scanning and angiography showed diameter reductions of more than 50 per cent, whereas pressure measurement did not show a haemodynamically significant lesion. Although difficult to answer, the question remains whether this was due to the non-existence of haemodynamically significant lesions, or inaccurate or wrongly interpreted pressure measurements.

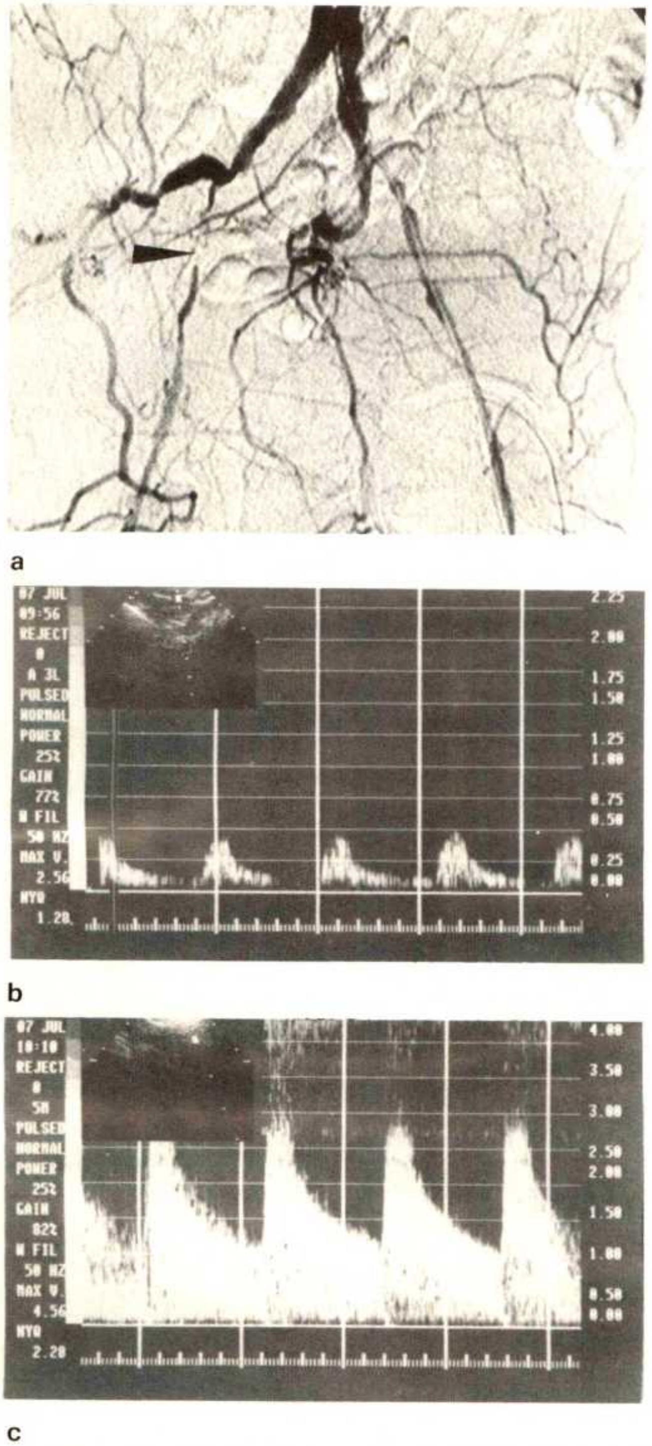

Figure 3 **a** *Angiogram showing a very tight stenosis in right external iliac artery;* **b** *Doppler ultrasound component of duplex scan for prestenotic segment* (Figure 3a). *Peak systolic velocity here is 0·5 m/s and end diastolic velocity is less than 0·1 m/s;* **c** *Doppler ultrasound component of duplex scan within the stenosis. Peak systolic velocity here is 3·0 m/s, peak systolic velocity ratio is 6·0, and end diastolic velocity is greater than 1·0 m/s. These values indicate a very high grade stenosis*

Separation into several subgroups of lesions by duplex scanning in the clinically important range of 50–100 per cent diameter reduction, as compared to angiography, was difficult. A very reliable separation could be made between an open or occluded arterial segment. However, differentiation based on clinically useful spectral cut-off levels between stenoses of 50–74 per cent and 75–99 per cent, based on a PSV ratio of greater than or equal to 5·5 and/or an EDV of greater than or equal to 0·6 m/s, was only possible in about half the cases. Although this might be due to limitations of the duplex scanning technique[19,20], it is noteworthy that the judgement of minor variations on the angiogram is itself subject to considerable interobserver variability[5,21,22].

The results of this study indicate that duplex scanning has reached the diagnostic standard of digital subtraction angiography in the detection of stenosis of greater than or equal to 50 per cent, and occlusion in the aortoiliac arteries, and may be considered a new and valuable diagnostic tool. IAPM after the administration of papaverine remains necessary if duplex scanning or angiography, in combination with the clinical symptoms of the patient, fails to suggest a haemodynamically significant lesion. A minority of such patients will show a significant drop in pressure gradient. However, in these patients a description of the exact localization of the haemodynamically significant lesions cannot be given. Furthermore, pressure measurements cannot differentiate between subtotal stenoses and occlusions, a distinction which can be important when choosing therapy. In this series, occlusion was demonstrated in seven aortoiliac segments by angiography; all were detected by duplex scanning. The duplex scan could even give an accurate description of the length of the occlusion in all cases.

Duplex scanning can be performed as an outpatient procedure and is entirely non-invasive. It is thus an ideal tool for the initial diagnostic investigation and for follow-up of patients with vascular disease. In our practice duplex scanning is becoming increasingly important in the assessment of aortoiliac lesions. Patients increasingly undergo duplex scanning before decisions are made to proceed with angiography. Although operative strategies are still based on angiographic findings, decisions about whether to proceed to percutaneous transluminal angioplasty or continue with an expectant policy are being based more and more on duplex scanning alone. In the future, it seems possible that, in selected cases, patients may undergo surgery solely on the basis of the duplex scan.

Duplex scanning measures blood flow velocity, which is flow-dependent, and in this way it has the potential to provide dynamic information similar to pressure measurement. In this study the duplex technique was only performed in the resting condition and the flow-independent PSV ratio was used to assess the severity of arterial lesions. Conceivably, duplex scanning performed following the non-invasive induction of reactive hyperaemia and the use of flow-related spectral analysis criteria may result in a diagnostic power equal to that of pressure measurement. However, flow-related diagnostic criteria for duplex scanning are not yet clearly defined, and further development of the technique should be focused on this area if improvement is to be made in judging the haemodynamic significance of arterial lesions. Only when this is achieved can the residual need for invasive IAPM be removed. Although this goal has still to be reached, the potential of duplex scanning to replace angiography in the detection of haemodynamically significant lesions has perhaps already been realized.

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Fibrinolytic activity and calf pump failure

The interstitial fibrinolytic activity of the upper and lower limbs was investigated in subjects with abnormal calf pump function by measuring the lysis rate of experimentally produced subcutaneous ^{125}*I-fibrin clots. Thirty-three subjects with healed venous ulcers, five with varicose veins and 11 controls were studied.* ^{125}*I-fibrin clots were produced in the subcutaneous tissue of the forearms and legs and clearance half-life was calculated. Calf pump function was assessed by foot volumetry and the 'gaiter' skin nutritive circulation by measuring the transcutaneous oxygen tension* (P_{tcO_2})*. Fibrin clearance was prolonged from the subcutaneous tissues of the legs of subjects with varicose veins and healed ulcers compared with controls. Negative correlations were found between fibrin clearance half-life and the half-volume refilling time* ($P<0{\cdot}01$) *and the* P_{tcO_2} ($P<0{\cdot}01$).

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The mechanism by which abnormal venous return leads to ulceration is not completely understood. The pericapillary fibrin cuffs which are found in lipodermatosclerotic skin are thought to block diffusion of oxygen and nutrients thus rendering the skin liable to ulceration, and their presence is thought to be related to a reduced level of interstitial fibrinolytic activity[1]. It is not known whether the defect in interstitial fibrinolytic activity is solely secondary to the abnormal calf pump function or whether there is an independent abnormality of fibrinolysis which determines the tissue response to an abnormal calf pump function. The aim of this study was to measure interstitial fibrinolytic activity, by measuring the lysis rate of experimentally produced subcutaneous ^{125}I-fibin clots, calf pump function and transcutaneous oxygen tension P_{tcO_2} to see if there is a relationship between them.

Patients and methods

Patients

Patients with healed venous ulcers were admitted to the study if they had normal serological investigations, a Doppler ankle–brachial pressure index > 1, and an abnormal calf pump function, thus excluding rheumatoid and ischaemic causes of ulceration and establishing venous disease as the cause. Patients taking anticoagulants or fibrinolytic enhancing agents were excluded as were women of child-bearing age. None of the patients with simple uncomplicated varicose veins gave a history of deep venous thrombosis or ulceration. The age and sex distribution of the patients and the control volunteers did not differ significantly.

Formation of radiolabelled fibrin clots

Radiolabelled clots were formed by the subcutaneous injection of 0·05 ml (0·2 MBq) ^{125}I-fibrinogen (Amersham International, Amersham, UK) followed immediately by 0·05 ml (200 units ml^{-1}) human thrombin (Plasma Fractionation Laboratory, Oxford, UK). These two substances were injected 4 mm below the surface of the skin of the mid flexor aspect of the forearm and the calf, 10 cm above the medial malleolus, through the same needle so that they mixed together around the tip of the needle. Subcutaneous veins, scars of previous ulcers and the subcutaneous border of the tibia were avoided. Radioactivity was measured using a collimated scintillation counter immediately after injection and therafter every 24 h for 96 h. Counts were corrected to take account of the physical half-life of the iodine-125. The half-life of the clearance curve was calculated for each injection site using linear regression analysis of a semilogarithmic plot of the corrected radioactivity against time.

Foot volumetry

Calf pump function was assessed by foot volumetry using a water bath plethysmograph constructed with modifications to the original design of Thulesius *et al.*[2] and closely following the method of Norgren[3]. Water bath displacement was sensed by measuring the change in conductance across two electrodes placed vertically in a side arm of the water tank[4]. This signal was amplified and passed to a pen recorder. Patients were studied in the morning after a 30 min rest period as there is evidence that calf pump function deteriorates during the day[5]. A baseline trace was made and the patient instructed to perform 20 knee bends keeping their foot flat in the water bath and their back straight, in time with a digital clock so that 20 knee bends were performed in 40 s. At the end of the knee bends, the patient stood still and the trace was allowed to return to the base line. After a period of rest, the test was repeated first with the patient wearing a narrow pneumatic cuff inflated to 100 mmHg above the knee then with the cuff below the knee. Both legs were examined in this way. The water bath temperature was maintained at 30°C as temperature has a considerable influence on ambulatory venous pressures[6]: below 30°C the expelled volume increases and the refilling flow decreases; above 30°C the refilling flow increases and the expelled volume decreases[3]. Five measurements of calf pump function were calculated from the trace shown in *Figure 1* (*Table 1*)[3].

Classification of venous insufficiency

Limbs were classed as having superficial vein incompetence if: (a) half volume refilling time ($TV_{1/2}$) and quotient (Q/EV_{rel}) were abnormal,

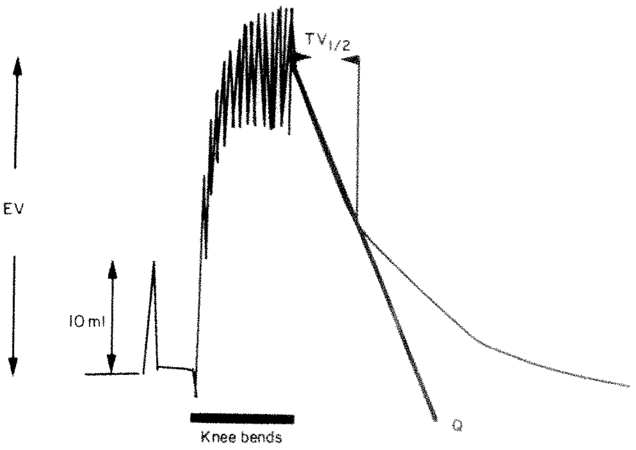

Figure 1 *Example of foot volumetry trace. Upward deflection of trace represents a fall in venous blood in the foot and lower calf. EV, expelled volume;* $TV_{1/2}$*, half-volume refilling time; Q, refilling rate after exercise in relation to foot volume*

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Table 1 *The five measurements of calf pump function (after Norgren*^{3}*)*

Expression	Abbreviation	Units
Expelled volume on exercise	EV	ml
Relative expelled volume; EV/foot volume × 100 ml	EV_{rel}	ml 100 ml^{-1}
Half volume refilling time	$TV_{1/2}$	s
Refilling rate after exercise in relation to foot volume	Q	ml 100 ml^{-1} × min
Quotient	Q/EV_{rel}	min^{-1}

but were restored to normal with a tourniquet; (b) relative expelled volume (EV_{rel}) was increased by a tourniquet[3,7].

Limbs were classed as having deep vein damage (deep venous obstruction or incompetence or perforating vein incompetence) if $TV_{1/2}$ and Q/EV_{rel} were abnormal and could not be restored to normal by a tourniquet at either level[3,7].

Our normal values for these measurements[7] using the equipment described are:

$TV_{1/2}$ 15–35 s
Q/EV_{rel} 0·7–2·3 min^{-1}
EV_{rel} 1·0–2·0 ml 100 ml^{-1}

Transcutaneous oximetry

The P_{tcO_2} was measured with a TCM2 transcutaneous oxygen monitor and Clarke-type electrode (Radiometer, Copenhagen, Denmark) between 08.00 and 10.00, with the patient supine, at a point 7·5 cm above the medial malleolus but away from any scars of previous ulceration, prominent veins or subcutaneous bone. Both legs were examined. The area was shaved if necessary and cleared with 70 per cent alcohol to allow good adhesive attachment of the electrode O-ring, which was filled with contact solution. Twenty minutes were allowed to elapse for the area of skin to heat to 45°C and for the readings to stabilize. Two measurements of P_{tcO_2}, in mmHg, were taken 20 min and 25 min after the electrodes were attached and the mean value recorded.

Results

Clearance of ^{125}*I-fibrin*

Both legs of 33 patients with healed venous ulcers (42 previously ulcerated limbs and 24 non-ulcerated limbs) and of five patients with bilateral uncomplicated varicose veins, but only one leg each of the 11 control subjects, were injected. There were no local complications.

The clearance of fibrin from the arms of subjects with varicose veins, healed venous ulcers and the controls did not differ significantly (*Table 2*). However, the clearance half-life of fibrin from legs with varicose veins, from non-ulcerated legs of ulcer patients and from legs with healed ulcers was significantly longer than that of the controls (Mann–Whitney *U* test; $P<0\cdot05$, $P<0\cdot05$ and $P<0\cdot01$ respectively; *Table 2*).

The difference between the fibrin clearance half-life from legs with healed venous ulcers and that from non-ulcerated legs of patients with venous ulcers was also statistically significant (Mann–Whitney *U* test; $P<0\cdot01$). The difference between legs with healed venous ulcers and legs with varicose veins did not quite reach statistical significance. There was no difference between non-ulcerated legs of ulcer patients and legs with varicose veins (*Table 2*).

Foot volumetry

Eleven control limbs, 10 limbs with varicose veins, 22 of 24 non-ulcerated limbs of ulcer subjects and 35 of 42 limbs with healed ulcers were examined by foot volumetry. Nine limbs could not be studied: one was too large for the water bath and eight had a fixed equino-varus deformity of the ankle joint that prevented the patient performing the knee bends satisfactorily. Four limbs with healed venous ulcers were studied without tourniquets because the patients found the tourniquets too uncomfortable.

The relative expelled volume (EV_{rel}) of the limbs is shown in *Table 3*. The relative expelled volume of legs with healed ulcers was significantly diminished compared with that of non-ulcerated legs of ulcer subjects ($P<0\cdot001$; Mann–Whitney *U* test). The half volume refilling time ($TV_{1/2}$) of legs with healed ulcers was shortened compared wth that of non-ulcerated legs of ulcer subjects and legs with varicose veins ($P<0\cdot01$; Mann–Whitney *U* test; *Table 4*).

Calf pump function was normal in all the subjects in the control group. The abnormal test result in limbs thought to have uncomplicated varicose veins was restored to normal by the use of a superficial tourniquet in five and very close to normal in four. The tourniquet did not improve the results in one of the limbs classified as having uncomplicated varicose veins.

Of the 35 limbs with healed venous ulcers, 21 were classified as having deep vein damage. One had normal $TV_{1/2}$ and Q/EV_{rel}, but low EV_{rel} which was not improved by the application of the superficial tourniquets, so this was included in the group with deep vein damage as was another which also had normal $TV_{1/2}$ and Q/EV_{rel} but the application of the superficial tourniquets greatly reduced the EV_{rel}. Ten limbs were classified as having simple superficial vein incompetence.

The relation between fibrin clearance half-life and foot volumetry

A statistically significant negative rank correlation was found

Table 2 *The half-life of clearance of fibrin from arms and legs*

	Half-life of clearance (h)		Significance compared with control limb*
	Median	Range	
Arms			
Control subjects	16	11–28	
Patients with varicose veins	16·5	14–21	n.s.
Patients with healed ulcers	17	11–29	n.s.
Legs			
Control subjects	15	13–27	
Varicose veins	23·5	18–37	$P<0\cdot05$
Non-ulcerated legs of ulcer patients	24·5	15–53	$P<0\cdot05$
Healed ulcers	31·5	16–121	$P<0\cdot001$

* Mann–Whitney U test. n.s., Not significant

Table 3 *The relative expelled volume of the lower limbs*

	EV_{rel} (ml 100 ml^{-1})		Compared with controls*
	Median	Range	
Controls	1·5	1·2–2·0	
Legs with varicose veins	0·65	0·3–1·7	$P<0\cdot05$
Non-ulcerated legs of ulcer patients	1·05	0·6–2·1	$P<0\cdot01$
Legs with healed ulcers	0·8	0·3–3·0	$P<0\cdot001$

* Mann–Whitney *U* test

Table 4 *The half-volume refilling time of the lower limbs*

	$TV_{1/2}$ (s)		Compared with controls*
	Median	Range	
Controls	18·0	13·5–60·0	
Legs with varicose veins	8·25	1·5–13·5	$P<0\cdot01$
Non-ulcerated legs of ulcer patients	6·0	1·5–30·0	$P<0\cdot01$
Legs with healed ulcers	3·0	1·0–22·5	$P<0\cdot001$

* Mann–Whitney *U* test

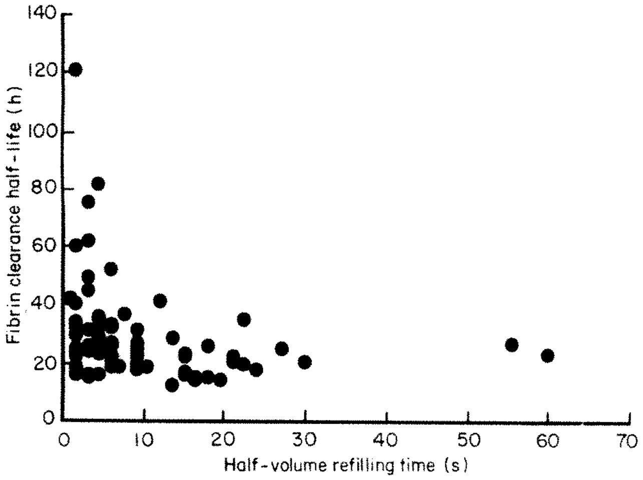

Figure 2 *Relationship between the clearance half-life of fibrin and the half-volume refilling time of all limbs. (Spearman rank correlation coefficient −0·29* ($P<0·01$))

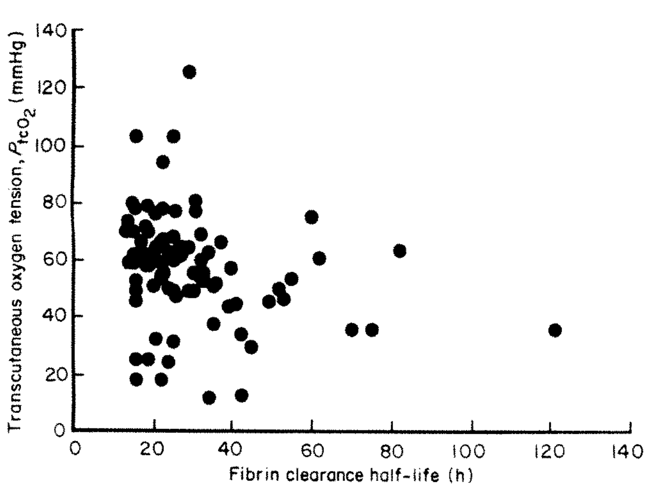

Figure 3 *Relationship between the clearance half-life of fibrin and the transcutaneous oxygen tension,* P_{tcO_2}, *of all limbs. (Spearman rank correlation coefficient −0·29* ($P<0·01$))

Table 5 *The transcutaneous oxygen tensions of the lower limbs*

	P_{tcO_2} (mmHg)		Compared with controls*
	Median	Range	
Controls	72	59–80	
Legs with varicose veins	68	58–126	n.s.
Non-ulcerated legs of ulcer subjects	59·5	25–103	$P<0·01$
Legs with healed ulcers	50·5	12–81	$P<0·001$

* Mann–Whitney *U* test. n.s., Not significant

between the fibrin clearance half-life and the half-volume refilling time (Spearman rank correlation $P<0·01$; *Figure 2*). The correlation coefficient of −0·29 shows this to be a weak correlation and suggests that the correlation is not linear but asymptotic. No correlation was found between the fibrin clearance half-life and the relative expelled volume.

The median fibrin clearance half-life from the group of limbs with healed venous ulcers classified as having deep vein damage was 30 h (range 16–121) and from the group with superficial venous reflux was 28 h (range 19–82). The difference was not statistically significant (Mann–Whitney *U* test). No correlation was found between the half-life of fibrin clearance and the $TV_{1/2}$ with the tourniquets applied, or between the half-life of fibrin clearance and the EV_{rel} with the tourniquets applied.

Transcutaneous oxygen tensions

The transcutaneous oxygen tension P_{tcO_2} of the limbs is shown in *Table 5*. A statistically significant negative correlation was found between the fibrin clearance half-life and the transcutaneous oxygen tension (Spearman rank correlation $P<0·01$; *Figure 3*). This is a weak correlation as shown by the Spearman rank correlation coefficient (−0·29).

Discussion

The use of ^{125}I-fibrin clots to measure interstitial fibrinolytic activity was first described in a pilot study[8] in 1982. The technique described in this paper differs in that the depth of injection has been standardized, a correction has been made to take account of the physical decay of the isotope and a half-life has been calculated from a series of measurements of radioactivity at the injection site taken over 96 h. It is impossible to be absolutely sure that the injection of ^{125}I-fibrinogen and human thrombin results in the formation of a cross-linked fibrin clot, but evidence from the pilot study suggests that it does: thrombin delays the disappearance of subcutaneous ^{125}I-fibrinogen and its omission leads to an increased rate of clearance and the appearance of radioactivity in the fibrinogen fraction of the blood, two observations that suggest that the fibrinogen is being altered and made less soluble. Markwardt and Nowak[9] have also found the use of localized microthrombi to be helpful in the study of the interstitial fibrinolytic activity of rats under various experimental conditions. They found that the rate of clearance of these clots was altered by manipulating the fibrinolytic system, suggesting that clearance was dependent upon fibrinolysis. The transit of relatively soluble subcutaneous proteins into lymph is more rapid from limbs with venous oedema than controls with no oedema[10,11]. We believe that these observations suggest that the injected fibrinogen is converted to fibrin and that its clearance is dependent upon the fibrinolytic activity of the interstitial fluid and not upon physical factors.

The clearance of fibrin from the arms of controls was not significantly different from that from their legs. The clearance of fibrin from legs with healed venous ulcers was significantly prolonged compared with legs which had never been ulcerated, and in turn the clearance of fibrin from these two sets of limbs was significantly prolonged compared with legs of control subjects. A statistically significant negative correlation was found between the fibrin clearance half-life and the half-volume refilling time. This association is consistent with but not proof of a causal relationship; however support for a causal relationship does come from the fact that the clearance of fibrin from the arms of controls, patients with varicose veins, and from patients with healed venous ulcers was not significantly different. It appears that the disturbance of fibrinolytic activity is confined to the lower limb with abnormal calf pump function and is not an independent determinant of the tissue response to venous hypertension. Prospective studies to examine the effects on the interstitial fibinolytic activity of attempts to improve calf pump function are under way and the results must be awaited before accepting a causal link between calf pump dysfunction and abnormal interstitial fibrinolytic activity.

The proportion of limbs with healed venous ulcers found to have either deep venous damage or superficial venous reflux was in keeping with previous work[12] and no significant difference was found between the fibrin clearance half-life and the half-volume refilling time of the limbs in these two groups. This suggests that the overall severity of the reflux is more important than its site (superficial or deep). The number of patients was small, however, and other work has emphasized the importance of deep venous reflux (particularly in the popliteal vein) in the pathogenesis of venous ulcer disease[13].

The present finding of reduced P_{tcO_2} in the legs of patients with ulcer disease agrees with previous work[14,15] and the negative correlation between P_{tcO_2} and the fibrin clearance half-life is in keeping with the fibrin diffusion block theory[1]. Further support has come from work by Stacey *et al.*[16] who, using a scoring system for the degree of fibrin cuffing around capillaries, have found a significant negative correlation between the fibrin score on histological examination of biopsy specimens and the P_{tcO_2} ratio among patients with venous ulcer disease.

These results are consistent with the hypothesis that calf pump dysfunction causes a reduction of interstitial fibrinolytic activity as well as an increase in capillary permeablity and that this reduction of fibrinolytic activity may be responsible for the deposition of interstitial fibrin which causes the reduced tissue oxygen levels. They also support the hypothesis, partly substantiated by clinical trials[17–19], that drugs which enhance fibrinolysis may improve lipodermatosclerosis.

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Cervical spine injuries in patients with head injuries

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It is generally believed that significant head injury after a traffic accident or fall is associated with a high incidence of concurrent cervical spine injury. This study prospectively examined 260 victims of traffic accidents or falls with significant head injury. The incidence of associated cervical spinal injury was only 3·5 per cent. There was no association between the severity of head injury and the incidence of cervical spine injury. The risk of concurrent spinal injury in head injury patients is not higher than the reported risk in patients without head injury. Although care should be taken to protect the cervical spine in patients with head injury, the results of the present investigation show that the risk of cervical spine injury is much less than previously reported.

It is generally believed that in patients with significant craniocerebral trauma there is a high incidence of associated cervical spine injury, in some series up to 20 per cent[1]. However, in a recent retrospective study, O'Malley and Ross[2] suggested that patients with serious head injuries were at no greater risk of cervical spine injury than patients without head trauma.

Patients and methods

A prospective study was conducted at Baragwanath Hospital, Johannesburg over a period of 4 months (January–April 1990). Included in the study were victims of traffic accidents or falls from a height with head injury. Patients had to have at least one of the following criteria for inclusion in the study: (a) loss of consciousness, (b) Glasgow Coma Scale (GCS) <12, (c) skull fracture. Patients who died soon after admission or before radiological investigation were excluded from the study. Initial radiographic assessment included anteroposterior and lateral views and computed tomography in appropriate cases. The cervical spine was assessed by means of routine radiographs. Open mouth views, stress views, tomograms and computed tomography were performed as indicated. Alart, sober, neurologically intact patients without neck symptoms or neck tenderness on palpation did not undergo cervical spine radiography. This policy has previously been shown to be safe[3]. The patients were followed up for a minimum of 7 days or until they were completely asymptomatic.

Head injuries with a skull fracture and/or a GCS <12 were regarded as severe. Patients with neck pain, stiffness or tenderness to palpation were regarded as having neck symptoms. Cervical injuries included fractures or dislocations of C1–C7. Soft tissue injuries were not included.

Results

Two hundred and sixty patients fulfilled the criteria for inclusion in the study. The average age was 25 years and 74 per cent were men. The causes of injury are shown in *Table 1*; 67 of the patients had a skull fracture, 55 had a GCS <12 and 247 had loss of consciousness. There were nine patients (3·5 per cent) with associated cervical spine injury. Five of these patients had neurological signs (quadriplegia in four and monoparesis in one) and the other four had only local neck symptoms, i.e. tenderness and/or stiffness. Seven of the cervical injuries involved the lower spine (C4–C7), one involved C2, and one was an injury involving C2, C6–C7. There was no correlation between the severity of head trauma and cervical spine injury. In none of the 67 documented skull fractures or the 55 patients with a GCS <12 was there an associated cervical spine injury. All nine neck injuries occurred in patients with relatively minor head injuries, i.e., transient loss of consciousness with a GCS >12 on admission. The incidence of associated neck injury in pedestrian accidents was 3·2 per cent and in car passengers 5·1 per cent. The difference was not statistically significant.

Discussion

The incidence of craniocerebral and/or cervical spine injury in fatal traffic accidents is very high. Alker *et al.*[4], in an autopsy study of 146 consecutive victims, found radiographically demonstrable skull fracture in 42 per cent and neck injury in 21 per cent. In a similar autopsy study of 100 cases, Bucholz *et al.*[5] reported an incidence of neck injury of 24 per cent. Bivins *et al.*[6] found an incidence of 24 per cent for neck injury in a series of 17 victims who died in the emergency department. On the basis of these reports it seems that approximately 20–25 per cent of victims dying immediately or soon after a traffic accident have a serious injury to the cervical spine. However, no study has ever shown any significant correlation between craniocerebral and cervical spine injury. In Alker's autopsy study the incidence of neck injury in the 61 cases with skull fractures was 16 per cent. Though this figure seems high, it does not necessarily indicate a significant correlation. These were victims of multiple trauma, often with injuries involving most anatomical parts of the body. Unfortunately, Alker does not mention the incidence of other associated injuries. Bucholtz, in his autopsy study of 100 cases, failed to show any statistically significant correlation between neck injury and head injury or trauma to any other part of the body[5]. Despite the lack of any scientific evidence, it is generally believed that victims of traffic accidents with head injury have a high incidence of associated neck injury. Most authors quote figures between 10 and 20 per cent[1,7]. It is obvious that these figures have been extrapolated from the published post-mortem studies.

Table 1 *Causes of injury in 260 patients*

Cause	No.	Percentage of total
Pedestrian trauma	126	48·5
Passenger trauma	79	30·4
Fall	38	14·6
Bicycle accident	11	4·2
Motorbike accident	4	1·5
Other	2	0·8
Total	260	100

However, it seems that spinal injury in traffic accident victims dying at the scene of the accident or soon afterwards is a different pathology from spinal injury seen in survivors. In early deaths the cervical spine injury typically involves the atlanto-occipital junction, C1 or C2, and it is often associated with head injury[4,5,8]. Spinal cord injury at this level is generally fatal, which may explain the various autopsy reports. In

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survivors the most common site of cervical injury is C4–C7, which is less likely to be associated with concurrent head injury[9].

The current view that 10–20 per cent of victims of blunt head injury have an associated cervical spine injury does not seem to be correct. For patients surviving more than a few hours this figure is most likely to be less than 4 per cent. O'Malley and Ross[2] retrospectively reviewed 1272 patients who sustained blunt trauma; 664 of them had a significant head injury and the incidence of associated cervical spine injury was 1·8 per cent. There were 608 patients without head trauma and the incidence of neck injury was 3·5 per cent. The authors concluded that patients with serious craniocerebral injury were at no greater risk of injury to the cervical spine than patients without trauma to the head. In the present prospective study we found an incidence of associated cervical spine injury of 3·5 per cent, the same as that reported for victims without head injury. Furthermore, there was no relationship between the severity of craniocerebral trauma and the possibility of associated cervical spine injury. There was no case of neck injury in the group of victims with a documented skull fracture or in the group of patients with GCS <12. All nine spinal injuries occurred in association with relatively minor head injury. During the same study period another six patients with cervical spine injury and no head injury at all were identified.

In conclusion, the incidence of concurrent cervical spine injury in patients with head injury due to a traffic accident or a fall from height is low. It is not higher than the reported incidence in patients without head trauma. Nevertheless, the same strict precautions should be taken in all victims of traffic accidents or falls, irrespective of the presence or absence of a head injury.

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Surgical workshop

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A new instrument: the toothed cutting forceps

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Skin closure with interrupted sutures contributes to a significant part of the total anaesthetic time. One cause of the time taken is that either the forceps or the needle holder must be put down so that the scissors can be used, and then picked up again for the next stitch. One alternative is to mount scissors on the needle holder (Gillies' needle holder); however, using this instrument, the needle is unmounted and therefore uncontrolled during a part of each stitch. Remounting the needle involves holding it between the fingers, risking needlestick injury and losing no-touch sterility.

A new instrument that saves time for unassisted surgeons is shown in *Figure 1*. It is similar to a Lane's toothed forceps, modified by carrying a pair of scissors within the central gap.

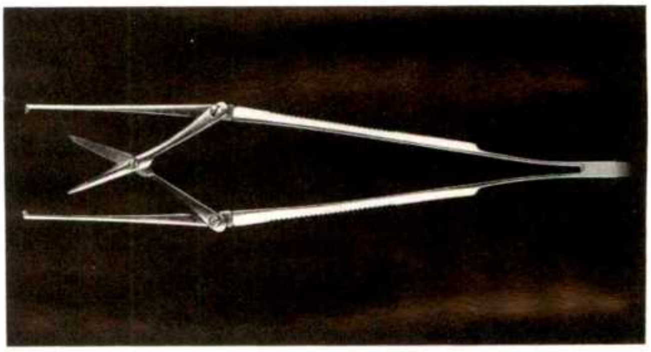

Figure 1 *Toothed cutting forceps (Rocialle Medical, Cambridge, UK)*

After the suture is placed and the knot tied by the right hand, the suture is cut with the forceps held in the left. The forceps are then in place to pick up the skin edge, with the left hand ready for the next stitch.

This instrument has also been found useful when two surgeons are closing wounds on either side of the table, as in bilateral varicose vein surgery, to enable either surgeon to cut each other's sutures without having to interrupt their own stitching.

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Pylorus-preserving 'cluster' operation

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Starzl *et al.*[1] have reported an extension of liver transplant operations to treat otherwise inoperable foregut tumours. A 'cluster' of organs is removed: the patient's liver, spleen, pancreas, stomach, upper small bowel and ascending and transverse colon. A donor liver, pancreas, duodenum and upper jejunum are then transplanted into the patient. This is a formidable undertaking and modifications of the implantation procedure have already been suggested by Starzl's group; for example, liver transplantation only and liver transplantation with injection of donor islet cells into the recipient's portal vein[2]. We report here a further modification of the cluster operation.

Patient and methods

The patient was a 47-year-old man who underwent an operation in September 1989 for a bile duct tumour. This was unresectable (without performing a total hepatectomy) because of exension of the tumour to involve both main hepatic ducts and both sides of the liver. No resection was undertaken and transtumoral intubation was carried out during surgery. However, several months later the patient developed recurrent jaundice and it was decided to carry out a total hepatectomy and transplantation. At operation in May 1990, the tumour was noted also to be invading the head of the pancreas. Therefore a resection was carried out of the liver, the structures in the portal pedicle, the pancreas, the spleen, the greater omentum and the splenic artery back to the coeliac axis. The common hepatic artery and left gastric artery were skeletonized and all associated tissue around them was removed with the specimen. A standard liver transplant was then carried out, except that the hepatic artery was anastomosed to the common hepatic artery of the recipient, closer to the coeliac axis than usual, and the donor bile duct was anastomosed to the recipient's jejunum with a Roux-en-Y loop. The stomach and pylorus were maintained, as in a pylorus-preserving pancreaticoduodenectomy, and were anastomosed to the jejunum 80 cm beyond the bile duct anastomosis (*Figure 1*).

Pathological examination of the specimen showed complete clearance of the tumour and also showed two separate bile duct tumours. The first was proximal and involved the liver as previously mentioned. The second was in the lower third of the common bile duct behind the pancreas.

The patient made a relatively uncomplicated recovery and was discharged from hospital 7·5 weeks after operation. At review in December 1990, the patient was well and had gained 2 kg in weight since discharge from hospital.

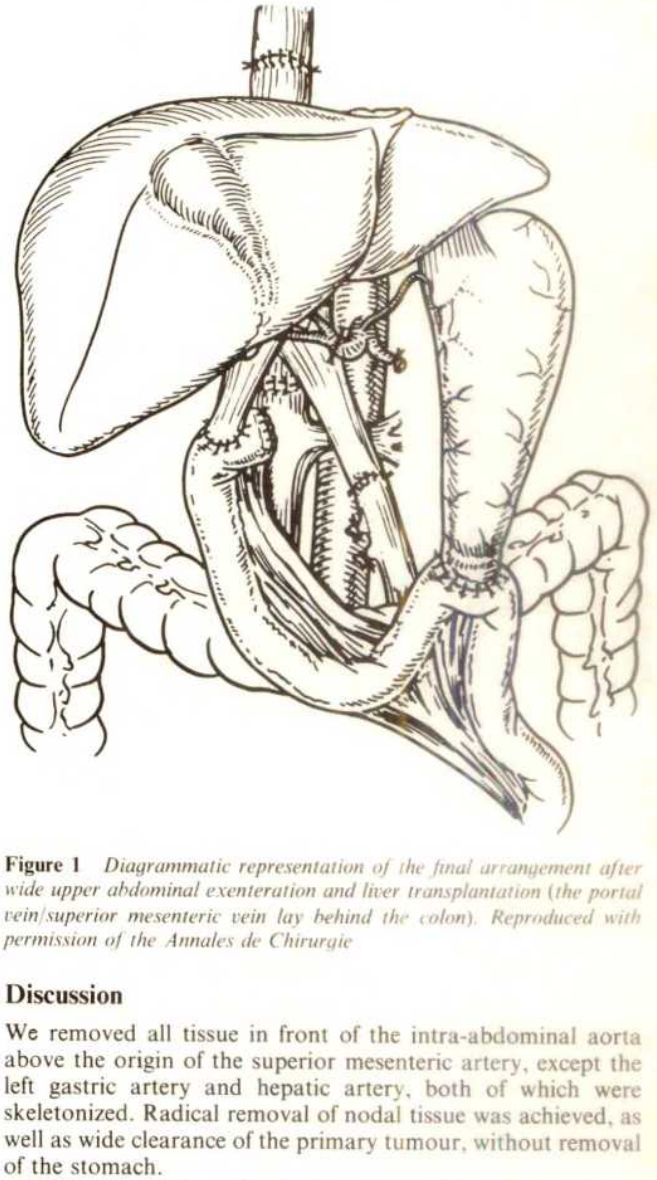

Figure 1 *Diagrammatic representation of the final arrangement after wide upper abdominal exenteration and liver transplantation (the portal vein/superior mesenteric vein lay behind the colon). Reproduced with permission of the Annales de Chirurgie*

Discussion

We removed all tissue in front of the intra-abdominal aorta above the origin of the superior mesenteric artery, except the left gastric artery and hepatic artery, both of which were skeletonized. Radical removal of nodal tissue was achieved, as well as wide clearance of the primary tumour, without removal of the stomach.

This approach reduced the complexity of the cluster technique. Furthermore, our experience with pylorus-preserving pancreatectomy leads us to believe that retention of the stomach might give an optimal nutritional result. Despite diabetes mellitus and the need for oral pancreatic supplements, the patient has gained weight and eats what he regards as normal meals. The long-term survival from such extensive resection remains to be determined.

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Paper acceepted 11 February 1991

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Surgical workshop

Br. J. Surg. 1991, Vol. 78, August, 1016–1017

New prosthetic venous collar anastomotic technique: combining the best of other procedures

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The poor outcome following polytetrafluoroethylene (PTFE) arterial reconstructions to single calf vessels is well recognised. Approximately one-third of these graft failures are attributable to the accumulation of anastomotic intimal hyperplasia[1]. The standard end-to-side PTFE arterial anastomosis is associated with an anastomotic compliance mismatch and arterial distortion, both factors which have been implicated in the formation of intimal hyperplasia[2]. Recently, Miller[3] and Taylor[4] have described new anastomotic techniques, both of which are associated with encouraging patency rates[5,6]. Nevertheless, both of these techniques have theoretical disadvantages; we have shown that the Miller collar produces severe turbulence because of its shape and the Taylor patch involves direct suturing of PTFE to the recipient artery at the heel so that intimal hyperplasia remains likely at this site. Each has its advantage; the Miller collar obviates the need for direct PTFE-arterial suturing, while the Taylor patch has a streamlined shape with a well pointed toe. We have designed a new vein collar intended to incorporate the advantages and eliminate the disadvantages of both of these techniques.

Methods

A short length of vein (approximately 6 cm) is harvested from any available source. The vein is then slit open lengthwise to yield a venous rectangle (*Figure 1*). The corner of the venous sheet is then sutured into the apex of the arteriotomy (using 7/0 polypropylene) to form the anastomotic toe (*Figure 2*). The remainder of the venous–arterial suture-line is completed in a fashion similar to the Miller collar, by draping the venous sheet around the full length of the arteriotomy (*Figure 3*). The redundant length of vein is excised obliquely (*Figure 4*) and the suture-line is completed to result in a boot-shaped venous reservoir. It is then necessary to tailor the heel of the boot by incising it posteriorly (*Figure 5*). Finally, the PTFE-boot anastomosis is carried out without difficulty and without any risk of stenosing critically narrow regions (*Figure 6*).

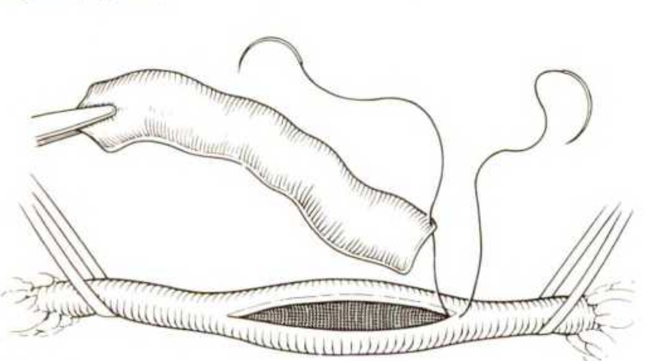

Figure 1 *A segment of vein has been split open longitudinally and one corner is anastomosed to the apex of the arteriotomy*

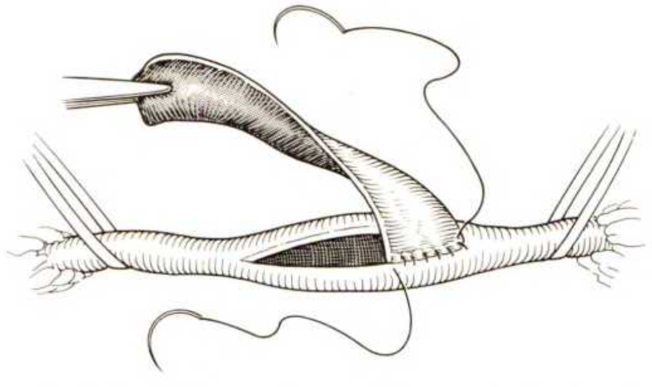

Figure 2 *The distal leading edge is anastomosed along the side of the arteriotomy*

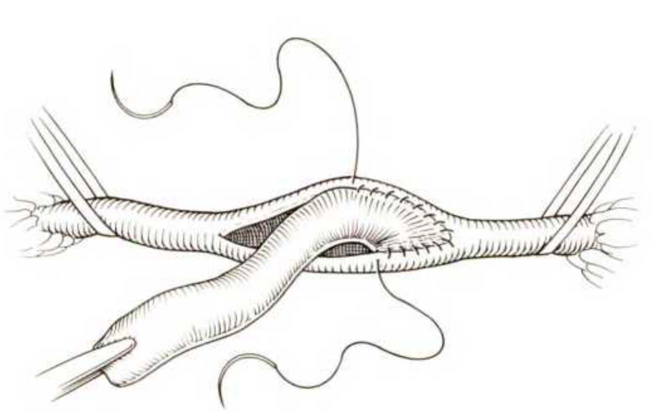

Figure 3 *The longitudinal length of vein is then anastomosed around the arteriotomy*

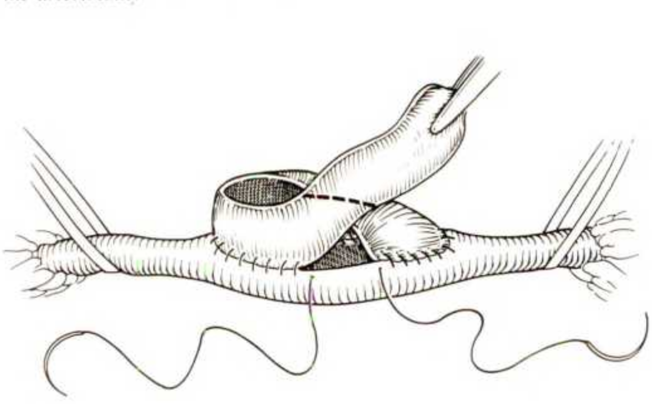

Figure 4 *A collar is formed and the redundant vein can be removed. The proximal edge of the vein collar is then anastomosed to the longitudinal edge*

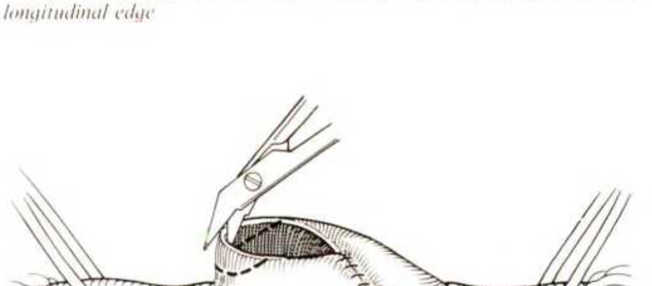

Figure 5 *A segment of posterior collar is incised to increase the size of the anastomosis between PTFE and vein collar*

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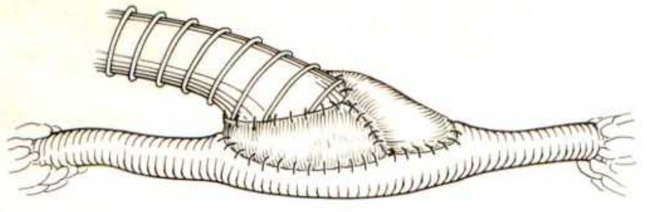

Figure 6 *The completed anastomosis*

Discussion

The heel and toe of any end-to-side anastomosis are particularly vulnerable to distortion and stenosis. While this distortion may be inconsequential in large vessels, it is probably crucial in the small tibial and peroneal vessels. There is evidence linking compliance mismatch with intimal hyperplasia and premature graft failure[2] and recent work suggests that an interposition vein collar reduces compliance mismatch[7]. Furthermore, examination of occluded Miller collars indicates that any intimal hyperplasia is restricted to the relatively large venous reservoir, with sparing of the recipient artery[8].

The Miller collar is likely to be associated with turbulent flow, but has no direct PTFE-arterial anastomosis. The Taylor patch probably allows more stable flow patterns, but involves a length of direct PTFE-arterial anastomosis (with its risk of intimal hyperplasia and premature graft occlusion). The new boot maintains a full compliant venous collar, avoids any direct contact between artery and PTFE, and maintains the haemodynamic advantages of the Taylor patch. It is hoped that these intended advantages will result in greater graft longevity.

Acknowledgements

The illustrations were prepared by Gillian Lee.

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The British Journal of Surgery – facts and figures

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Authors of papers submitted to *The British Journal of Surgery* are often concerned that there is a delay in the editor reaching a decision about their article, and equally editors are aware of the discontent among authors about that delay. As all original articles are sent to two referees, there is a minimum turnaround time for an original article. During 1990, 1287 articles were submitted to the *Journal*: 810 were rejected and 374 were accepted with the remainder still in the hands of the author or editor. Of the rejected original articles ($n = 320$), the median time to rejection was 50 days (range 1–344 days); for case reports ($n = 233$), for which referees were not always consulted, the decision was reached by the editor within a median of 3 days (range 1–119 days). Surgical workshop ($n = 23$) and other articles ($n = 34$) had a median time to rejection of 8 and 44 days respectively.

For the 257 original articles published in 1990 there was a median time from acceptance to publication of 164 days (range 53–250 days), giving a time from submission to publication of 281 days (range 70–790 days) (*Figure 1*). Editorial ineptitude is not the explanation for the enormous range for, in a random sample of 20 original articles where the author was asked to resubmit, the articles were returned in a median of 108 days (range 21–50 days) – so much for impatient authors. Case reports fare better, in that the 27 reports published in 1990 waited 190 days (range 132–294 days) from acceptance to publication with a submission to publication of 267 days (range 171–690 days).

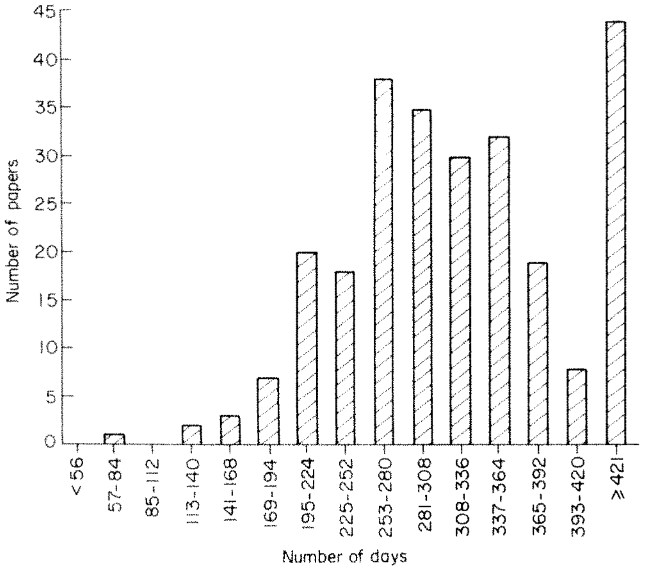

Figure 1 *Number of days between submission and publication for original articles published in 1990 (median 281 days)*

Table 1 *Number of pages published in the* Journal *between 1984 and 1990*

Year	Pages	Increase in pages from previous year	Percentage increase on previous year	Percentage increase on 1984 number
1984	1024	264	–	–
1985	1042	18	2	2
1986	1064	22	2	4
1987	1205	141	13	18
1988	1294	89	7	26
1989	1378	84	6	35
1990	1454	76	6	42

To save the budding author difficult decisions about the number of references suitable for an article, this has been calculated. The 26 leaders published in 1990 had a mean of 8 references (range 4–26); the 23 reviews had a median of 80 references (range 19–174), while the 257 original articles had a median of 17 references (range 4–101). Case reports should and did have less references (median 6; range 2–16) as did the short notes (median 8; range 1–18).

The number of authors, and who should be included as an author, has given rise to comment in the *Journal* previously. The general principle that only those directly contributing to the concept, the work and the writing of the article should be included remains true; thus leaders had a median of 1 author (range 1–3, and reviews 2 (range 1–5), while original articles had a median of 4 authors (range 1–10).

The subject matter published in the *Journal* varies in emphasis from year to year according to the winds of surgical fashion. Papers on coloproctology remain the most popular in 1990 (49 accepted) with arterial papers second (42 accepted) and gastroenterology (38) and hepatobiliary (35) following close behind. These four are followed by oncology (20), general topics (19), breast (16), oesohagus (16), venous (14), nutrition (13), pancreas (13) and surgical technique (12). The remaining papers covered 19 separate topics.

The papers come from many countries, 166 being from England, 7 from Wales, 39 from Scotland and 21 from Ireland. No less than 39 per cent of the papers come from outside the UK: 13 from each of South Africa, Sweden, USA and the Netherlands, and 12 each from Germany and Japan.

To accommodate these papers, and to provide the authors with a steadily improving service, the *Journal* has increased in size (*Table 1*) so that month by month the reader has received a thicker, more varied, and hopefully a higher quality *Journal*.

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Correspondence

Reduced postoperative hospitalization after laparoscopic cholecystectomy

Sir

The brave attempt by Grace *et al.* (*Br J Surg* 1991; **78**: 160–2) to compare laparoscopic with conventional cholecystectomy suffers from several defects.

First, the numbers in the two groups should have been equal because a few complications or long stays in 25 patients can effect the picture considerably.

Second, it is misleading to compare operating times when only one group had peroperative cholangiograms (followed by exploration of the common bile duct for unsuspected stones in 8 per cent).

Third, details of the surgeons performing the operations should have been given. Presumably experienced surgeons performed the laparoscopic procedures, but did they also perform the 25 standard procedures? A standard cholecystectomy without a cholangiogram, performed by an experienced surgeon in the type of patient that was chosen for laparoscopic cholecystectomy, would not have a median anaesthetic time of 102 min.

Fourth, why did the laparotomy group stay in hospital for a mean of 9 days after operation? Many large studies of standard elective cholecystectomy show the mean stay as 5–6 days.

Finally, few details are given about how costs were calculated. How was operating time costed and how was the £250 per day derived?

The key question, however, is what the patients were told about their expected length of stay and time off work. I recently had an intelligent patient referred from another district for laparoscopic cholecystectomy because she had been told that if she had a conventional operation she would not be able to drive a care for 4 months! Until these widely held myths are dispelled, it will be difficult to make any realistic assessment of how much time and money can be saved by the laparoscopic procedure. Once we are comparing like with like, I suspect there will be a trade-off between a longer operating time and a little shorter hospital stay.

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Author's reply

Sir

We thank Professor Johnson for his interest in the paper. We agree that the gold standard for assessing any new technique is the randomized controlled trial. The difficulties of undertaking a randomized controlled trial to compare laparoscopic with conventional cholecystectomy have been extensively reviewed by Neugebauer and colleagues[1]. These authors concluded that 'the response of surgeons and patients to the new procedure (laparoscopic cholecystectomy) now place ethical constraints on the planning of a randomized controlled trial'. Similar concerns followed the widespread application of ESWL for renal calculi in the 1980s[2]. However, we felt obliged to evaluate the impact of laparoscopic cholecystectomy in our hospital. Thus, rather than simply report our initial experience with laparoscopic cholecystectomy, we compared our first 50 patients with the best group of historical controls available to us, i.e. the last 25 patients who had undergone laparotomy cholecystectomy at our hospital. The ratio of 2:1 has frequently been used when assessing new techniques, particularly when one wishes to discover whether the new technique is better than a standard technique[3].

We have explained our philosophy regarding peroperative cholangiography for potential common bile duct stones at some length[4]. The anaesthesia time for laparoscopic cholecystectomy, already significantly longer than anaesthesia time for laparotomy cholecystectomy, would have been even longer had we undertaken peroperative cholangiography in these patients. Both laparotomy and laparoscopy operations were performed by the same group of surgeons, and the fact that 22 per cent of the laparoscopy patients had an acute gallbladder refutes the suggestion that we preselected the patients for laparoscopic cholecystectomy.

We were surprised that our mean postoperative hospital stay after laparotomy cholecystectomy was 9 days, and clearly this was a major contributor to the cost of laparotomy cholecystectomy in our study. This is a reflection of the social background of our patient population, and this observation has acted as a stimulus for evaluation of the reasons for longer hospital stay in our community.

Laparoscopic cholecystectomy is currently being performed in some centres on a day-case basis[5]. An analysis of our last 25 patients showed that the procedure now takes the same length of time to perform as the traditional cholecystectomy. Thus, the operating room costs are now identical for the two procedures. Moreover, several authors have demonstrated that the time until resumation of full activity after operation is substantially decreased following laparoscopic cholecystectomy[6,7]. Thus we believe that laparoscopic cholecystectomy confers significant economic advances to the patient, the hospital, the health provider and the community.

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Surgical management of primary hyperhidrosis

Sir

We enjoyed Moran and Brady's objective and factual review of the surgery of primary hyperhidrosis (*Br J Surg* 1991; **78**: 279–83), and would endorse their comments regarding the morbidity of this condition.

In the past 4 years we have performed 36 endoscopic thoracic sympathectomies on 20 patients, 13 of whom had hyperhidrosis[1]. Despite the fact that we consider ourselves to be on the learning curve with this procedure, we have had no permanent complications apart from numbness in the intercostobrachial territory on two occasions. The 25 sympathectomies performed for hyperhidrosis produced immediate improvement in all cases, and this has been sustained in all but one patient. Forty-five per cent of our patients have exhibited compensatory hyperhidrosis, but this is considered to be only a minor nuisance. The mean postoperative stay was 3 days, and all patients were delighted with the cosmetic result.

Moran and Brady quote Malone in stating that 63 per cent of patients present with palmar symptoms, two-thirds of these also having axillary symptoms In our experience of this condition, 11 of 13 patients (85 per cent) complained of palmar sweating. As palmar hyperhidrosis is curable only by sympathectomy, it follows that surgery is the appropriate modality of treatment for the majority of referrals. Indeed, we have found endoscopic sympathectomy to be equally effective in the management of axillary hyperhidrosis.

It is interesting to note that after we had performed a staged procedure, all patients were keen to proceed to the contralateral operation. These data contrast with Sternberg's findings that 23–27 per cent of patients having a successful unilateral open procedure would not consider having the other side treated because of the postoperative pain[2]

We concur with Messrs Moran and Brady that upper thoracic sympathectomy is the appropriate management of palmar hyperhidrosis, but would further suggest that the endoscopic method is the surgical procedure of choice in both axillary and palmar hyperhidrosis.

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Intra-arterial thrombolytic therapy in the management of acute and chronic limb ischaemia

Sir

The reporting of results of treatment by peripheral thrombolysis is bedevilled by a deficiency of agreed criteria for defining a successful outcome The publication of the recent experience of intra-arterial thrombolysis in Reading (*Br J Surg* 1991, **78**. 284–7), although welcomed, illustrates this since the terms 'complete lysis', 'effective lysis' and 'successful lysis' are not defined in the text Our patients are described as having undergone successful lysis only if the following five criteria are met. (1) limb salvage at 30 days; (2) radiological evidence of thrombus lysis with vessel recanalization at least as far as the next major collateral, (3) an increase in ankle·brachial index of at least 0 2 maintained to 30 days; (4) no clinical evidence of re-thrombosis; (5) no surgery at the level at which lysis is performed.

If these criteria are applied to the Reading series, the rate of successful lysis appears to be less than 50 per cent. This is in line with our experience using streptokinase, and emphasizes the scope for improved results with this type of treatment

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Author's reply

Sir

Mr Lonsdale apparently regards intra-arterial thrombolysis (IAT) as a therapeutic measure only. Dissolution of thrombus may identify an underlying causative lesion which can subsequently be dealt with either by surgical reconstruction or angioplasty

We have recently reviewed the first 82 occlusions treated by IAT in Reading[1] In half of those in which IAT cleared the thrombus or embolus, a significant underlying lesion was identified which was then corrected. By using IAT in these cases we were able subsequently to revascularize the limb with a lesser procedure than might otherwise have been necessary The role of IAT in clearing thrombosed popliteal aneurysms is becoming increasingly recognized[2,3]. Using the criteria described by Mr Lonsdale, clearance of popliteal aneurysms and their run-off followed by ligation and bypass of the aneurysm, would presumably be regarded as 'failure of lysis'. On the other hand, those cleared but then treated conservatively would be claimed as 'successful lysis' I would suggest that lysis has been equally successful in each of these two circumstances.

Although there is clearly a need for establishing criteria to define outcome, omission of the diagnostic role of IAT would considerably understate its value

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Experimental study of starch-induced intraperitoneal adhesions

Sir

I was interested to read the letter by Eynon and Thomson (*Br J Surg* 1991, **78**. 377) Intestinal adhesions are almost inevitable after any laparotomy. We found that 93 per cent of 210 second-look laparotomies had adhesions which resulted from previous surgery[1] There are many causes for this. including any factor which produces peritoneal ischaemia or the presence of irritating foreign materials[2] Starch is an important one among a large number of other possible aetiological factors. Eynon and Thomson query the role of the lubricating material on starch-free gloves However, the lubricant, a hydrogel polymer, is actually bonded to the inside surface of the glove, cannot be detached and, in any case, our experiments at Westminster showed that pieces of glove material bonded to hydrogel polymer failed to induce adhesions in the peritoneal cavity of the rat.

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1 Menzies D, Ellis H Intestinal obstruction from adhesions – how big is the problem? *Ann Roy Coll Surg Eng* 1990; **72** 60–3
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Book reviews

Basic Cutaneous Surgery

C. B Zachary 152 × 229 mm Pp 128 Illustrated, 1990 New York Churchill Livingstone. £17 50

This is a very well presented manual, the latest in a series of American publications covering aspects of surgery of the skin and appendages Published in paperback at a reasonable price of £17.50, and in a convenient size for reference, it covers a considerable range of techniques of excision and biopsy of skin lesions and the repair of the resultant defects The market targeting is clearly for surgical trainees and dermatological specialists rather than for aspirant or practising plastic surgeons, and those who work in the American system of office practice will be appreciative of a clear presentation of the considerations to be made before skin surgery and the plastic techniques involved

The opening chapter deals with the general considerations involved in skin surgery, with special reference to case selection, counselling, notes on instrumentation, preoperative sedation and local anaesthetic agents. The drug names are, of course, transatlantic but should be recognizable to well-read European practitioners. There are useful tips on prevention of complications, and the suggestion of postoperative instruction sheets to remind patients of verbal advice is welcome. The subsequent chapters are progressively more technical, ranging from simple suturing to advanced flaps, with useful and practical suggestions for the small extra measures that can give an adequate operation an excellent result Management of 'dog-ears' and tension-relieving manoeuvres are well described The line drawings are excellent, and are well supported by concise and clear text which is easy on the eye Step-by-step descriptions of flap technique simplify undertanding of the more complex procedures such as multiple Z-plasty, rhomboid and bilobed flaps, and I especally liked the guidance notes on timing suture removal for the best cosmetic results.

This book will be welcomed by dermatology trainees and surgeons called upon to support their less aggressive dermatology colleagues It would be nice to think that it will find a place in the libraries of Accident Departments and Operating Suites There will probably also be a market, in this area of the new contract, for GPs who may find the guidance contained in this volume invaluable.

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Advances in Surgery, Vol. 24

J L Cameron, C M Balch, B. Langer, J A Mannick, G. F. Sheldon, G T Shires, R. K Tompkins and C E. Welch 229 × 152 mm Pp 398 Illustrated. 1991 St Louis Mosby Year Book £42.50

Volume 24 of *Advances in Surgery*, as with previous volumes in this series, paints a broad canvas Twelve chapters, in 398 pages, consider malignancy in the form of soft tissue sarcomas, melanoma and rectal cancer, haematological problems including thrombolytic therapy, coagulation disorders and immunotherapy, strategies for vascular reconstruction, the evaluation of trauma patients, surgery in the elderly and the current management of gastro-oesophageal reflux and pancreatic abscess The book has an undoubted North American flavour, reflecting its contributors. Beware of judging this book on the basis of its first contribution, entitled 'Current options in the management of rectal cancer' There is little here that improves Golligher's observations, and there are but a few lines on recent developments such as adjuvant treatment, laser therapy and biological markers of tumour aggression There are several operative diagrams which are taken from Maingot's textbook Perioperative radiotherapy is discussed well, but there is virtually nothing on palliation in rectal cancer and only a few comments about on-table lavage

By contrast, the chapter on modern immunotherapy of cancer is good, covering many trials and the use of cytokines in a variety of soft tumours and solid cancers Mention is made of monoclonal antibodies, immunoconjugates, vaccines and recombinant cytokines.

It is encouraging to see the reintroduction of the surgical debate in two consecutive chapters, arguing both for and against autogenous tissue for vascular bypasses below the inguinal ligament The data is well presented in both chapters

The chapter on 'Thrombolytic therapy' provides details of established and new drugs, their mechanisms of action, and contraindications, and which patients should receive them

Solzhenitsyn's 'queen of malignant tumours' (malignant melanoma) is very nicely reviewed in an up-to-date discussion of how to approach the suspicious lesion and how to stage it both by traditional and also new methods (DNA ploidy). There is a good section on recurrence of malignant melanoma and its treatment, including chemotherapy, biological response modifiers and radiotherapy The operative description of how to do an axillary node dissection could be read with benefit by those surgeons treating breast cancer

The chapter on the current managment of oesophageal reflux emphasizes the difficulty in making this diagnosis on occasions and the need for careful investigation, including pH monitoring The pathophysiology of the sphincter disorder is reviewed well

The physiology of ageing and the preparation of the biologically aged patient for surgery is adequately discussed in the chapter on 'Surgery in the aged'

Soft tissue sarcomas of the extremity and the retroperitoneum are rare and their aetiology is discussed in the chapter which deals with this. Up-to-date information on the retinoblastoma gene is included in this chapter, as is the important information that the medical profession is not good at making this diagnosis

The chapter on 'Current management of pancreatic abscess' discusses the transition from pancreatic necrosis to infection and ways to make this diagnosis.

In summary, this book provides a series of interesting chapters which on the whole are well written and researched.

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Clinical cancer monographs, Vols I, II and III (Oesophagus, Larynx and Stomach)

Mathews et al. *Robin* et al, *Fielding* et al. *240 × 155 mm Pp 184 Illustrated. 1987 Southampton· Macmillan-Stockton Press.*

These three monographs are timely After 1 April 1991, all doctors in the UK will move into the era of regular audit, and all medical activities and outcomes will be subject to review These three books describe cancer management in the West Midlands The data bases for the three reviews are similar; the Cancer Registry in Birmingham has collected data routinely since 1957, the data is validated and 99 88 per cent complete The geographical area covered by this data collection has remained unchanged and the authors have good demographic data to underpin their endeavours The clinical and statistical data presented here are unique and accurate

There are three monographs *Oesophageal Cancer*, which has a clinical input from Hugoe Mathews; *Laryngeal Cancer*, outstandingly displayed in a comprehensive commentary by Peter Robin, and *Stomach Cancer*, reviewed by John Fielding The combination in each monograph of clinical and epidemiological expertise works well Although each book is different in style, the basic presentation is succinct and comprehensible The volumes on oesophageal cancer and stomach cancer will obviously appeal to the surgeon/gastroenterologist However, the volume on laryngeal cancer, which will appeal to ENT surgeons and surgeons with a head and neck interest, needs special mention General surgeons and surgeons with an academic bent will find it very attractive and it deserves to be widely read

These three excellent monographs are ideals for us all to achieve if we are going to improve British surgery by the simple expedient of finding out what we do and how well we do it

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UNIVERSITY COLL

Liver Transplantation: A 31-Year Perspective

T. E Starzl and A J Demetris. 155 × 235 mm Pp 194. Illustrated. 1990 London Year Book Medical Publishing.

Books heralded as a classic in the field tend to disappoint This one does not

This volume of current problems in surgery draws together three extended reviews, published previously, into a 31-year experience of liver transplantation by the experienced medical group led by Dr Thomas Starzl. Almost every important aspect of modern hepatic transplantation is covered, including the preliminary data on FK 506, and the historical prospectives are clearly outlined and informative

Although many of the illustrations appeared in the primary papers or monographs, many appear to have been redrawn and show a clarity that many contempoary books should emulate. It would, however, be helpful if they were all the right way up!

Although a small volume of less than 200 pages, the wealth of experience outlined in the chapters will be of invaluable assistance to clinicians active in the field, and the extensive contemporary references are most helpful.

As they say, no liver transplant unit should be without it!

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Surgery Annual 1991. Part 1

L M Nyhus, ed 235 mm Pp 237 Illustrated 1991 Connecticut Appleton & Lange. $75 00.

As Dr Nyhus states in his preface 'this is a new look Surgery Annual in that it comes in two parts. Part I is devoted to a series of chapters on clinical surgery while Part II will portray a basic science flavour to include features on experimental peptic ulceration and primary hyperparathyroidism to name but two' This separation would suggest the importance of these volumes as a means of keeping busy surgeons up to date, and for researchers to reap the reward of others' toil from the assembly of surgical references.

The stated aim of this volume is to present topics of interest for several specialities and to embrace an international flavour. This is partially achieved by including chapters from South African and Japanese surgeons.

The subjects covered range through perioperative paediatric surgical care, current surgery for melanoma, two articles on biliary disease, endoscopic obliteration of oesophageal varices, and colonic and head trauma. The chapters on melanoma and oesohageal varices are particularly good and the whole volume is suggested reading for any Fellowship candidate

The offering on the economics of general surgical deaths might interest NHS Hospital Managers and Clinical Surgical Directors but it was not to my taste. It did not need to be told that surgical emergencies who die quickly cost less than those who linger Even with Independent Trusts looming, it was a harsh and disturbing piece

The highlight comes from John A Collins in his overview of surgery for 1991 – some 29 pages and 241 references. This is a 'tour de force' and not to be missed by any surgeon wishing for a sharp, racy and in places cynical account of '1990 and all that'. 'All that is printed is not gold', states Collins, and, while disagreeing with the reviewer for 1990, he deliberately includes some examples of poor scholarship and indifferent hasty work, hoping, I guess, to shame intending authors, peer assessors and editors to do rather better Anyone interested in the fragility of surgical fashion will be pleased to note that laparoscopic cholecystectomy is totally defunked, as is biological predeterminism in breast cancer. He is particularly severe about local excision for that prevalent disease, and the whole review of breast matters is refreshing and clear After all, a flagrant oxymoron is the term 'minimal breast cancer' I found it was a superb piece of writing, full of common sense and eminently informative. He even extends his barbs to the philosophy of junior staff training and the ethos of hard work; shades of the late Ian Aird.

Perhaps, at $75 this is a book to view in the library, especially for the trainee, but very worthy overall I enjoyed it

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Year Book of Vascular Surgery

J J. Bergan and J. S. T Yao 235 × 155 mm. Pp 316. Illustrated. 1990. Chicago Year Book Medical Publishers Inc

Once again, Bergan and Yao, together with eight contributing editors, one of whom is British, have produced another splendid collection of abstracts from publications in *Vascular Surgery* in the year up to July 1989 This well-known series has become essential reading for the vascular surgeon and those in training taking up a career in this specialty. This latest edition has 309 abstracts of papers grouped in 24 chapters which cover all aspects of vascular surgery. European papers are well represented in this volume, but as might be expected North American papers do predominate

There is a good cross-section of reviews on aortic aneurysm, particularly on screening and management of problem aneurysms There are major chapters on recent advances in femorodistal surgery and on the investigation and management of cerebrovascular disease. There are relatively fewer articles on basic considerations, aetiology and prevention in vascular disease Perhaps this is not surprising as in the past vascular surgeons have tended to concentrate more on diagnosis and management than on these other aspects Disappointingly, there are relatively few abstracts on new developments, particularly on the use of interventional radiology and non-surgical treatments such as fibrinolytic therapy which have been gaining prominence in the management of vascular disease in recent years

Venous disease is not forgotten, with a good selection of abstracts on management of caval problems, developments in venous reconstruction, the management of primary varicosities and chronic venous insufficiency. The lymphatics merit only three abstracts and the volume finishes up with a few recent publications on portal hypertension, which, in the UK, is not usually dealt with by the vascular surgeon

This volume gives a useful overview of progress in vascular surgery in the recent year, and should be on the shelf of every departmental library where vascular surgery is undertaken

J. Chamberlain

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Notices and announcements

5–6 September 1991
Pancreatic Meeting: Progress and Prospects
Southampton, UK
Information Mrs June Daniels, Unit Administrative Secretary, University Surgical Block, F Level, Southampton General Hospital, Southampton SO1 6HU, UK

19–20 September 1991
Tissue Viability Society Autumn Conference
London, UK
Information Mr J Gisby, Tissue Viability Society, Wessex Rehabilitation Association, Odstock Hospital, Salisbury, Wilts SP2 8BJ, UK

20–23 September 1991
60th Annual Meeting of the Royal College of Physicians and Surgeons of Canada
Quebec City, Quebec, Canada
Information Anna Lee Chabot, The Royal College of Physicians and Surgeons of Canada, 74 Stanley, Ottawa, Canada K1M 1P4

24–26 September 1991
5th International Symposium on Colorectal Cancer
Turin, Italy
Information Francorosso Health Congress, c/o Jet Viaggi, Corso Matteotti, 1, 10121 Torino, Italy

2–4 October 1991
12th International Symposium on Computer Assisted Decision Support & Database Management in Anesthesia, Intensive Care and Cardiopulmonary Medicine
Rotterdam, The Netherlands
Information Dr Omar Prakash, Thorax Centre, Erasmus University, 3000 DR Rotterdam, The Netherlands

2–5 October 1991
Course in Surgical Oncology; Royal Marsden and Westminster Hospitals
London, UK
Information The Manager, Education and Conference Centre, Royal Marsden Hospital, Fulham Road, London SW3 6JJ, UK

7–10 October 1991
5th Congress of the European Society for Organ Transplantation
Maastricht, The Netherlands
Information Congress Secretariat, Conference Agency Limburg, c/o University Hospital Maastricht, PO Box 1918, 6201 BX Maastricht, The Netherlands

9–12 October 1991
Principles of Colon and Rectal Surgery
Minneapolis, Minnesota, USA
Information Continuing Medical Education, University of Minnesota Medical School, Radisson Hotel Metrodome, Suite 107, 615 Washington Avenue Southeast, Minneapolis, Minnesota 55414, USA

20–25 October 1991
American College of Surgeons Annual Clinical Congress
Chicago, USA
Information Sally Gerneski, American College of Surgeons, 55 East Erie Street, Chicago, Illinois 60611-2797 USA

30 Oct–3 Nov and 3 Nov–6 Nov 1991
International Conference of Gastroenterology
Hong Kong then Beijing, China
Information Conference Secretariat, 12/F Kaiseng Commercial Centre, 4–6 Hankow Road, Kowloon, Hong Kong

5–8 November 1991
Intensive Practical Course in Phlebology
Houston, Texas, USA
Information N A S P, 204 N. El Camino Real, E-234, Encinitas, CA 92024, USA

7 November 1991
'Vascular Training Would Be Improved By A Specific Diploma'
London, UK
Information Mr J H N Wolfe, Secretary, London Vascular Debating Group, St Mary's Hospital, Praed Street, London, WC2 1NY, UK

7–9 November 1991
3rd Combined Meeting of the Nederlandse Vereniging voor Thoraxchirurgie and the Deutsche Gesellschaft für Thorax-, Herz- und Gefasschirurgie
Maastricht, The Netherlands
Information Organizing Secretariat, Conference Agency Limburg, University Hospital Maastricht, PO Box 1918, 6201 BX Maastricht, The Netherlands

7–10 November 1991
XVII European Society for Medical Oncology Conference
Lyon, France
Information Michel Clavel, MD, XVII Congress ESMO, CLB, 28, rue Laennec, 69373 Lyon Cedex 08, France

8 November 1991
Vascular Symposium. Angioplasty, Thrombolysis & Angioscopy — A Minimally Invasive Approach to Arterial Disease
Edinburgh, UK
Information Mr C V Ruckley, University Department of Surgery, Edinburgh Royal Infirmary, Edinburgh EH3 9YW, UK

12–14 November 1991
1st European Conference on Tissue Banking and Clinical Application
Berlin, Germany
Information Mr Rudiger von Versen, German Central Tissue Bank, ITT, Medical Faculty (Charite), Humboldt-University Berlin, Schumannstr 20/21, D-1040 Berlin, Germany

14–16 November 1991
10th Annual WBAMC Trauma Symposium
El Paso, Texas, USA
Information Mrs Marty May, Trauma Service/SICU, Department of the Army, William Beaumont Army Medical Center, El Paso, Texas 79920–5001, USA

15–16 November 1991
Laparoscopic Cholecystectomy Workshop
Edinburgh, UK
Information Mrs Maureen Webb, Royal College of Surgeons of Edinburgh, Nicolson Street, Edinburgh EH8 9DW, UK

17–23 November 1991
Surgery of the Pancreas, Liver and Biliary System
Edinburgh, UK
Information Courses Department, The British Council, 10 Spring Gardens, London SW1A 2BN, UK

3–5 December 1991
6th International Workshop on Therapeutic Endoscopy
Hong-Kong
Information Dr J. W. C Leung, Department of Medicine, The Chinese University of Hong Kong, Prince of Wales Hospital, Shatin, Hong Kong

12–13 December 1991
1st EEC Conference on Pain Research
Brussels, Belgium
Information M Staquet, Rue Heger-Bordet, 1, B-1000 Brussels, Belgium

5–8 January 1992
Postgraduate Gastroenterology Course
Oxford, UK
Information Dr D P Jewell, Radcliffe Infirmary, Oxford OX2 6HE, UK

JULY 1991/VOLUME 162/NUMBER 1

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OFFICIAL PUBLICATION OF
The Society for Surgery of the Alimentary Tract
The North Pacific Surgical Association
The Society for Clinical Vascular Surgery
The Society of Head and Neck Surgeons
The Southwestern Surgical Congress
The Association for Surgical Education

Contents

EDITORIAL OPINION

1 **Continued Comments on Changes in the Education of Residents in Surgery**
Paul Friedmann, Ward O. Griffen, Jr., Roland Folse, and Hiram C. Polk, Jr.

SCIENTIFIC PAPERS

4 **Color Doppler Ultrasound Imaging in Iatrogenic Arterial Injuries**
Robert A. Schwartz, David B. Kerns, and Donald G. Mitchell

9 **Acute Appendicitis in Patients with AIDS/HIV Infection**
Sander R. Binderow and Abraham A. Shaked

13 **Weight Control After Vertical Banded Gastroplasty for Morbid Obesity**
Charles E. Yale and Stephen J. Weiler

19 **Bypass Grafting to the Popliteal Artery in Limbs with Occluded Crural Arteries**
Sadettin Karacagil, Bo Almgren, Staffan Bowald, and Ingvar Eriksson

24 **The Allen Brown Shunt: A Useful Option for Vascular Access**
Warwick J. Adams, John F. Thompson, Betty Liounis, Henrik Ekberg, and Irene Rotenko

31 **Effect of Bile Diversion and Sphincterotomy on Gallbladder Muscle Contractility and Gallstone Formation**
Yong F. Li, Norman W. Weisbrodt, and Frank G. Moody

36 **Computed Tomographic Scan Confirmation of Paraprosthetic Enteric Fistula**
Robert S.D. Higgins, David L. Steed, Albert B. Zajko, Jules Sumkin, and Marshall W. Webster

39 **Value of Computed Tomography of the Lung in the Management of Primary Spontaneous Pneumothorax**
Brad W. Warner, Warren W. Bailey, and Ralph T. Shipley

43 **Insulinopenia as a Risk Factor in Hepatectomy and Its Resolution by Intraportal Insulin Administration**
Keiichiro Mori, Kazue Ozawa, Tetsuya Kiuchi, Yasutsugu Takada, Tetsuya Yamaguchi, Tetsuo Sadamoto, Yasuyuki Shimahara, Nobuaki Kobayashi, Yoshio Yamaoka, and Kaoru Kumada

50 **Late Follow-Up of Carotid Endarterectomy With Venous Patch Angioplasty**
Sachinder Singh Hans

55 **Hemodynamics in the Prone Jackknife Position During Surgery**
Takuya Hatada, Masato Kusunoki, Tooru Sakiyama, Youichirou Sakanoue, Takehira Yamamura, Ryu Okutani, Katsuakira Kono, Hiroatsu Ishida, and Joji Utsunomiya

59 **Hydroxyethyl Starch Macromolecule and Superoxide Dismutase Effects on Myocardial Reperfusion Injury**
Mehmet C. Oz, Bashir A. Zikria, Paul F. McLeod, and Sulli J. Popilkis

ASSOCIATION FOR SURGICAL EDUCATION

63 **Pass/Fail Grading: A Disadvantage for Students Applying for Residency**
John A. Dietrick, Michael T. Weaver, and Hollis W. Merrick

67 **The Structured Oral Examination as a Method for Assessing Surgical Residents**
Dimitri J. Anastakis, Robert Cohen, and Richard K. Reznick

70 **Editorial Comment**
Donald Trunkey

HOW I DO IT

71 **Avoidance of Bile Duct Injury During Laparoscopic Cholecystectomy**
John G. Hunter

77 **External Annular Prosthesis in Repair of Biliary Tract Stricture**
Marco Alarcon-Ramos

BRIEF REPORT

83 **Changing Patterns in the Morbidity and Mortality of Colorectal Surgery**
Jonathan Nwiloh, Herbert Dardik, Michael Dardik, Luke Aneke, and Ibrahim M. Ibrahim

90 **Letters to the Editor**

92 **Book Reviews**

A12 **Society Meetings**

A12 **Announcements**

A13 **Classified Advertising**

A14 **Classified Advertising**

A15 ***The British Journal of Surgery* Table of Contents (vol. 78, no. 6, June 1991)**

A16 **Information for Authors**